Revolutionizing Standard Operating Procedures in Biomanufacturing

by

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Submitted to the MIT Sloan School of Management and the Department of Engineering Systems in Partial Fulfillment of the Requirements for the Degrees of

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Abstract

In its quest to become a High Reliability Performance (HRP) organization, Amgen manufacturing operations desires to further improve its adherence to, and effectiveness of, its standard operating procedures (SOPs). SOPs are expected to provide clear guidance to operators to enable them to perform their job safely and effectively. This thesis aims to take a step back and answer the question "What is the best way to provide information and instruction to floor operators in order for them to perform their job in the best way possible?" Our hypothesis is that SOPs with content and style customized to the needs of the user will enhance performance along key operational metrics.

This thesis includes an analysis of the current challenges of Amgen's existing SOPs including comparison to external benchmarks and academic research. Subsequently, we provide a recommendation on future SOP content, style and supporting infrastructure informed by our research. The analysis concludes with the results of a pilot project designed to evaluate our hypothesis. The analysis indicates that while our initial findings are encouraging, further research is required to conclusively determine the validity of our hypothesis.

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1 Introduction

The information presented in this thesis is the result of an internship with Amgen, Inc. from June to December 2012. Amgen's Manufacturing Technologies group sponsored the internship to study the manufacturing network's Standard Operating Procedures (SOPs) and propose improvements or alternatives that would improve operational performance. The two main opportunities identified to address current weaknesses in SOPs were content and format. Concurrently, organizational enhancements surrounding how SOPs are developed and managed were also studied.

Over the course of the six-month engagement, we evaluated the current SOP structure across multiple sites, researched alternative implementations in academic literature and base-lined external industries to develop a future state proposal for SOP content, format and implementation. We leveraged Amgen expertise across multiple sites and functions to clarify our ideas. We tested our ideas in a live manufacturing setting through a pilot program thereby evaluating the validity of our hypothesis.

This section covers a general and specific description of the problem, a brief explanation of our hypothesis, a description of our research methodology followed by a chapter by chapter outline of this thesis.

1.1 General and Specific Problem Description

Every organization that employs people to conduct activities faces challenges with human performance. There is no simple formula to continuously improve productivity while maintaining high standards of quality and service. Manufacturing organizations in particular have a host of concerns that act as constraints against unchecked improvements in productivity. Some of these concerns include personnel safety, product safety, product quality, compliance to regulations, labor laws, etc. It is easy to improve productivity by relaxing quality controls but this is unacceptable. Instead, organizations need to find other more nuanced ways to improve productivity. Some of these include supervision, training, procedures, organizational design, product and system design, work processes, etc. Each of these tools

plays a role in helping the organization enhance productivity but not at the expense of quality, safety and the other constraints listed above. Like many manufacturing organizations, Amgen desires to improve the performance of its organization – to become a High Reliability Performance (HRP) organization. Through the umbrella of HRP, Amgen is tackling challenges in supervision (through the Purposeful Presence on the Floor (PPoF) program) and in training (through the Global Training and Qualification Program (GTQP)).

Though Amgen has, and continues to make, good progress towards becoming a HRP organization through its current initiatives, there is an opportunity to revolutionize the way it constructs and uses Standard Operating Procedures (SOPs). The aim of this internship and this thesis is to propose a new approach to SOPs relevant to Amgen in the context of a biomanufacturing environment. Specifically, we desire to improve productivity on the floor while maintaining a high standard of quality and compliance. Standard Operating Procedures have attracted attention as a significant barrier to wholesale improvements due to their current nature. Though it is equally important to look at improvements in training as well as supervision (the other parts of HRP), we are choosing to focus on SOPs in this thesis. Enhancements to the training and supervision programs are being handled through other projects at Amgen (Global Training and Qualification and Purposeful Presence on the Floor respectively). We worked closely with the other initiatives to ensure we have alignment but the focus of our endeavor is SOPs.

Current SOPs are typically developed by staff (in an office environment) who have less current experience performing jobs on the line than their operator counterparts. As a result of this, the organization and level of information in current SOPs does not necessarily match the needs of the operator on the plant floor. Current SOPs are organized around different equipment types (e.g. bioreactors) or concepts (equipment labeling). In order to perform a specific task on the floor one that requires the interaction of multiple components and concepts, the operator needs to juggle numerous SOPs. Since the primary author of the SOP is not the operator, the level of detail provided in SOPs does not always match the needs of the customer (operator). Oftentimes, SOPs balloon in length with details

surrounding background information, roles and responsibilities, troubleshooting information, and other content not related directly to the work at hand. Summarily, from a content perspective, SOPs are not as directed and concise as they should be.

Separate of the content itself, current SOPs provide information in a written report format regardless of the needs of the operator or the task to be performed. Current SOPs are typically long word documents with extensive prose (though often bulleted). This prose is supplanted with a few pictures or illustrations but those are more the exception than the rule. Complex tasks involving numerous decisions or spatial configurations are treated the same as simpler tasks - with instructions provided in black typeface on a white page. In choosing the way in which information is presented to the operator, the organization treats all tasks the same. Indeed, given that text heavy procedures are a standard across industries it is easy to see why alternative approaches might not have had much traction. A one size fits all approach is not an effective solution for SOP format.

Like many manufacturing organizations, Amgen faces the challenge of improving the productivity of its workforce while maintaining operational, quality and regulatory standards. SOPs are one lever to accomplish this but current SOPs are cumbersome to use. They are often abundant in excessive details and require excessive work on behalf of the operator to get the information they need for the job at hand to be performed 'right first time'. What Amgen needs is an approach to improve SOPs such that it sees corresponding improvements productivity, quality and compliance.

1.2 Hypothesis

Our hypothesis is that by tailoring the design of SOPs to the needs of the user and their task, we can improve performance along key metrics such as productivity, quality and compliance. This redesign of SOPs will be accomplished through a two-pronged approach:

- **Content:** focus the content on clear and concise instructions for the task at hand
- **Style:** choose a way to present the information that is consistent with the needs of the task and user

Both of these approaches are consistent with a user-centric design philosophy. By adopting a user-centric (and task centric) philosophy we expect to see improvements in operator performance, which will lead to productivity and quality gains. Additionally, this approach should make SOPs easier to use thereby improving our compliance metrics as well.

1.3 Research Methodology

In researching this thesis, we adopted a multiphase approach as described below:

- **Current state analysis:** Before investigating possible solutions to the issue at hand, we endeavored to understand the current state of the organization and its processes to the best of our ability. This allowed us to dive deep into the issue at hand and investigate the nature of the problem and possible contributing factors. The success of our approach depends on our ability to customize our solution to the needs of the organization as much as possible. This included numerous interviews and research across multiple plants and geographies.
- **External baselines:** Once we had a clear picture of the issue at hand, we looked outside Amgen for inspiration. This external investigation consisted of two types:
    - *Other industries:* The problem Amgen faces with SOPs and human performance is a universal one that cuts across all manufacturing organizations. We selected the aviation and nuclear industry to investigate since, like Amgen, they perform complex operations in a highly regulated environment.

- *Academic research:* We looked to past research done by experts in safety, human factors, leadership, and manufacturing operations. This provided us with a rigorous foundation on which to build our ideas of a new future state for SOPs at Amgen.

- **Future state development:** Armed with the knowledge from our external baselines, we worked to develop a future state for SOPs at Amgen. We made sure to consider the SOPs themselves as well as the organizational environment they inhabit. Stakeholders from all the key parts of the organization (floor operators, quality, manufacturing, document management, senior leadership, and engineering) were involved in the process to ensure the feasibility of our proposed solution.
- **Pilot program:** In order to test our hypothesis/future state solution, we developed a pilot program to evaluate if we could see real gains implementing our methods in a live manufacturing environment. Working closely with operators, we developed prototypes of SOPs using our new approach to replace current SOPs in a running plant. A key aspect of our approach was using the operator's floor experience and needs to guide the content and structure of the prototype SOPs. We then base-lined the current performance of the plant along key metrics (qualitative and quantitative) so that we could measure the appropriate change when we put in place our new SOPs. After completion of the pilot, we analyzed the data to see what it could indicate about the validity of our hypothesis in addition to any other findings of note.

1.4 Thesis Outline

In chapter 2, we provide a summary of past work in the area of procedures and human performance from academic literature.

In chapter 3, we investigate how other industries provide instructions to their staff on the floor. The industries we chose to evaluate are aviation and nuclear since they, like Amgen, perform high reliability operations in a highly regulated environment.

In chapter 4, an overview of the biotechnology and Amgen is provided. Following, we focus on company organization and the manufacturing group in particular.

In chapter 5, we discuss the motivation behind this internship project. We cover the origins in the Defense in Depth program, concerns raised around procedures and compliance and lastly feedback from the users on the floor.

In chapter 6, we go into detail about the current state of standard operating procedures at Amgen. We investigate their place in the organization, the other types of information that exist, and how this information is managed and presented. We discuss the current link between procedures and training as well as past improvement efforts.

In chapter 7, we introduce the future state proposal for SOPs and the surrounding ecosystem. User centric and task based philosophies form the foundation for the proposal to change both content and style for SOPs. We offer multiple procedure types for consideration based on the nature of the job at hand. With the future procedure architecture defined, we discuss how it relates to other systems, quality and compliance considerations and the interface with training and qualification. Lastly, we have a brief discussion on the technology considerations for the more sophisticated aspects of the new architecture.

In chapter 8, we discuss the pilot program from conception through execution. Specific considerations and constraints in scoping, site selection, prototype development, and execution are presented.

In chapter 9, we present the results of the pilot program. We see both quantitative as well as qualitative data – which when combined provide a holistic view of the program. We discuss possible trends and indicators from the data and their limitations.

In chapter 10, conclusions of our research are offered and recommendations for future work are made.

2 Literature Review

There is not a lot of research that has been published specific to the area of procedure improvement and human factors in a biomanufacturing context. However, work has been done in different contexts about how procedures are used, the impact of excessive details and the role of procedures for different tasks including troubleshooting. This is some of the research that we will explore in this chapter.

2.1 How procedures are used

In many organizations (including Amgen), procedures are authored by technical experts. These technical experts are often engineers who have a deep knowledge of equipment and processes but not necessarily an abundance of experience on the manufacturing floor. In *The 3 cultures of Management*, Schein argues that "Decisions have to be put into a form that lower levels can understand often resulting in 'translations' that actually distort and sometimes even subvert what higher levels wanted" (Schein). These communication gaps can easily translate into lost efficiencies and process risk.

Beyond authorship, the update process for operating procedures is another avenue for risk introduction. We have already briefly discussed in this thesis how the tendency to attribute non conformances (NCs) to procedure deficiency and the subsequent desire to close out these NCs with procedure revisions drives the addition of additional information and details in the procedure. In *Managing Risks of Organizational Accidents*, Reason argues

"Safe operating procedures are continually being amended to prohibit actions that have recently been implicated in some recent accident or incident…Over time, these additions to the 'rule book' becoming increasingly restrictive, often reducing the range of permitted actions to far less than those necessary to get the job done under anything but optimal conditions…After each event, the procedures are modified so as to proscribe these implicated actions. As a consequence, the scope of allowable actions

gradually shrinks to a range that is less than required to perform all the necessary actions. *The only way to do these jobs is to violate the procedures*" (Reason).

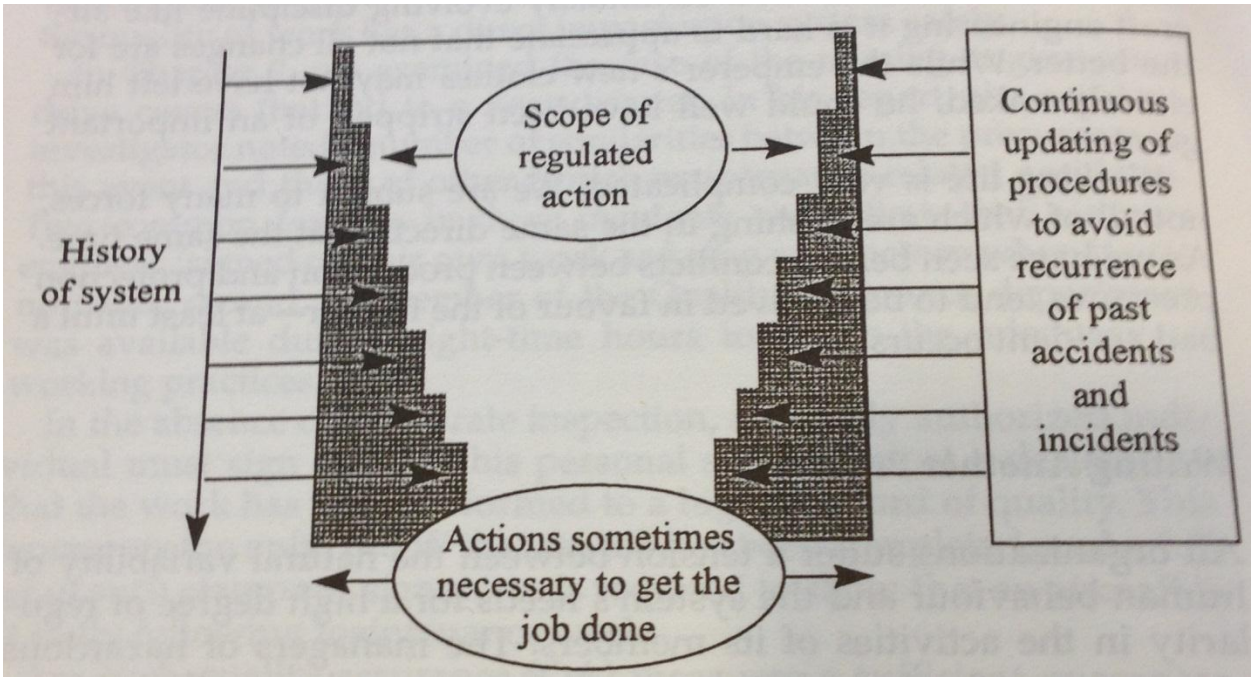


Figure 1: Scope of action due to procedure updates

The figure above shows how the scope of regulated actions can hamper an operator's ability to take action. According to Reason, a procedure violation itself is not harmful since many times the only way to perform the job adequately is to violate an over specified procedure. In his mind, procedure violations are not errors but can increase the likelihood that errors will lead to unwanted consequences since the process is not in control: "A [procedure] violation plus an error is frequently a formula for disaster in hazardous work." Reason states that repetition of procedure violations in isolation does not usually bring about bad outcome. These violations are just one cause among a complex interaction of latent conditions, local triggers and active failures. This is realized quickly by the workforce as they continue to violate procedure on the path towards efficiency. Violations are now routine. But Reason also points out that violations may not guarantee a bad outcome, they do increase the risks. They increase the risk of error and the likelihood error will lead to bad outcome. This argument directly supports the need for compliance to procedures in operations. Compliance, however, will only lead to desired outcomes if the procedures that

are being followed are robust. On the subject of the origin of errors, Reason argues "Errors arise from underspecification of various mental operations, many violations are created by procedure overspecification" (Reason).

Reason is not alone in arguing that excessive details in procedures can hamper an operator's ability to carry out their job. Perin offers the following anecdote in *Shouldering Risk*:

> "In response to Three Mile Island, Électricité De France (EDF) dramatically increased the use of procedures and automation in the operations of the plant. This made things extremely complicated and cumbersome. "*Without realizing it, we gradually transformed the actions and operations to be carried out into a complicated path to follow…strewn with obstacle…never ending traffic signals…the attention of the people to carry out the actions was progressively diverted to the specific details of the path to be followed thus losing sight of the purpose and reasons for the operation…Unintentionally, we had succeeded in transforming people…into "programmed machines"…*" In the years that followed, operational incidents at EDF plants were linked to overly prescriptive procedures among other factors" (Perin).

From the above discussion, it is reasonable to expect operators to encounter scenarios where the requirement to ensure a successful outcome is at odds with the requirement to follow the procedure. In cases like this, operators will often violate the procedure to achieve their goals. This shift in thinking represents a movement from rule-based mode (following the procedures) to knowledge-based mode (relying on training and knowledge) which is where errors are most likely to occur. These are "errors of intention", where "operators intend to perform an action that is incorrect but that they believe to… represent a superior method of performance" (Mosneron-Dupin, et al). The only way to minimize errors is to ensure the right level and kinds of information are covered in procedures as well as training.

2.2 Procedures and training

It is not always clear what information needs to be communicated to staff through training and what should be documented in standard operating procedures. As Reason notes, "It is, after all, much cheaper to have the work performed by a relatively untrained labor force controlled by procedures than it is to rely upon the judgment of experienced and highly trained individuals" (Reason). However, not all tasks readily lend themselves to being 'proceduralized'. Perrow argues that there are two aspects that determine the degree to which a task can be pre-programmed (Perrow):

- The number of 'exceptional cases'; i.e. the degree to which surprises, novel situations, and unexpected events are likely to arise
- The nature of the 'search process' required to deal with problems. Some problems may be easily resolved by analysis and application of rule-based solutions; others are little understood and require extensive knowledge-based processing

The fewer exceptional cases and knowledge based processing required, the easier it is to develop procedures that operators can completely rely on. Reason recognizes the duopoly between procedures and training (or knowledge based processing):

"There are 2 components to the administrative controls that form a part of any system's defenses:

- **External controls:** rules, regulations and procedures that prescribe what actions may be performed and how they should be carried out. Such paper-based controls embody the system's collective wisdom on how the work should be done.
- **Internal controls:** derived from the knowledge and principles acquired through training and experience" (Reason)

Training represents the feedback model of learning: knowledge from past experiences is incorporated into training to allow the operator to be better prepared to handle unknown situations. Procedures

represent the opposite – a feed-forward model of learning. Procedures are the collective knowledge of the system instructing the operator on how to exactly perform their job. Reason points out "The longer and more intensive an individual's training, the less likely is that person to be governed by rigid feed-forward controls, and conversely." This makes intuitive sense since better-trained operators theoretically would chafe more at being restricted in their ability to take appropriate actions to ensure success. This is true in almost any profession with the exception of airline pilots and the military where feed-forward controls are ingrained in the culture. Well-trained operators have little patience for procedures that provide instructions inferior to what their knowledge of the task tells them to do. Good procedures are correct but also further personal goals (efficiency, least effort). The converse is true for bad procedures (Reason).

Given that procedures and training have to share the responsibility for providing information to staff, a good candidate to move from procedures to training is the responsibility for troubleshooting. "The variety of possible unsafe behaviors is very much greater than the variety of required productive behaviors... thus the requisite variety of the procedures necessary to govern safe behavior will always be less than the possible variety of unsafe situations". The implication is that is impossible to develop a rule-based solution to troubleshooting and the solution should largely be knowledge-based. This is reflected in the fact that we need to engage more of our conscious mind for troubleshooting (a key tenet of knowledge-based situations). Reason goes on to argue that "wholly safe behavior can never be controlled entirely by feed-forward prescriptions …there will always be bad rule or no rule situations." In other words, strict guidance on responses to upset situations can limit the operator actions in unforeseen circumstances to their danger and the danger of the process. Certain complex tasks can never be completely proceduralized and the organization will have to look to their training prescription as a suitable compliment (Reason).

2.3 A multifaceted approach to human performance

In *The A+B+C method*, Smith proposes that human error in operations can only be minimized by developing a holistic plan of attack managing A (level of procedure detail), B (worker's level of knowledge) and C (amount of supervisory involvement). Smith's research was based on the nuclear industry which explains the resemblance of the A+B+C method to the three pronged approach of Amgen's High Reliability Performance initiative. Smith argues that focusing on any single aspect is not sufficient to bring about lasting improvement in the process and significant reduction in human error rates (as opposed to equipment error rates) (Smith). Through HRP and this thesis, we are applying some of Smith's thoughts to a different environment: biomanufacturing.

3 Case studies from other industries

In this chapter, we discuss in detail how two other industries, aerospace and nuclear, handle their SOPs. We chose to benchmark these industries (as opposed to many others) for the following reasons:

- **Reliability:** Like biotech, these industries perform complex and critical operations. Any upset to the process would have serious quality and safety consequences to patients, passengers or the local municipality.
- **Regulations:** While Amgen contends with the FDA, the aerospace and nuclear industries have the FAA (federal aviation administration) and the NRC (nuclear regulatory commission) to deal with.
- **Technology:** All three industries continue to push the edge of current technology and applications within their field. The sophisticated nature of their products makes these industries all 'high-tech'.
- **People centered:** Even though they embrace technology and automation, all three industries still have people at the core of their operations. Trusting people to execute complex tasks based on provided guidance is a common thread for biotech, aerospace and nuclear.

Given the above reasoning, we considered the aerospace and nuclear industries as good benchmarks. Additionally, given that these industries are older than the biotech industry, they very likely offer some wisdom that comes with experience. In this chapter, we will understand how a major aerospace company and a major nuclear operator deal with issues around SOPs and human performance in their organizations.

3.1 Aerospace (Company A)

- **Procedure content:** On their most up to date production lines, Company A uses an integrated electronic system to provide high level instructions. Typically, manufacturing technicians (MTs), the floor operators, receive procedures in the form of a few high level steps. Other information in

terms of reference diagrams and materials is provided as links through the system at various levels of technical sophistication. It is important to note that these references (be they specs or drawings/diagrams) are provided specific to the job at hand. In other words, the specific relevant paragraph from the spec is extracted in the hyperlink rather than forcing the MT to peruse the entire specification (which contains exhaustive technical information on a particular topic or piece of equipment). The particular details about how to perform the task are not explicitly specified. Rather, Company A relies on its work teams on the floor to determine the best way to perform a task. As a result, the knowledge of 'how' to perform a task is captured through on the job training, mentoring, and knowledge transfer in the style of master to apprentice. This enables the operators to be well skilled in their job but makes job rotation and knowledge transfer/preservation difficult since each team creates their own procedures and processes with very limited documentation. This system encourages local innovation but makes it difficult to onboard new members to the group. For procedures, revisions are not common due to the high level nature of the instruction and few details. At the same time, standard work is difficult to implement as the specific way to perform a task is not documented.

- **Company A Specs:** Company A has a number of technical specifications (i.e. specs) that contain knowledge related to technical tasks and requirements across all their lines. While procedures are authored by manufacturing engineers, specs are important enough to be authored by internal engineering experts. These specs are referenced in their procedure system and MTs are required to periodically train on specs to ensure their knowledge is up to date. However, these specs are concerned with outcomes rather than techniques (no standard work). They are written by engineers to provide the technical foundation on the topic at hand. As a result these specs typically do not get revised very often. Procedures are allowed to be high level instructions because it is assumed that all MTs are knowledgeable and familiar with the specs. Of course, specs are always available for reference.

- **Procedure style:** As mentioned, Company A uses an electronic system to provide instructions to MTs. Paper versions of these instructions are rarely printed out due to concerns about out-of-date information. The instructions themselves are usually text driven with visuals as needed. Where new 3D technology has been implemented, MTs have the ability to have a custom 3D visual for the job at hand they can interact with. The MTs usually access the system (and the 3D visuals) from a desktop workstation near their work area (tablet functionality is in the works).This interaction yields useful information such as location mapping, materials, and multiple perspectives for the task. All instructions (including 3D) are developed in house by Company A manufacturing engineers using a purchased software package. With the 3D technology there is a learning curve for both development and use. It is a dramatic departure from paper instructions and drawings of the past. However, feedback from engineers and MTs indicates that they are up to the challenge.

- **System design:** On their latest line, Company A uses an integrated electronic system for design, planning and execution. As a result, procedures are delivered electronically to teams and management is able to know who performed what task and when. Their training system is integrated into this system as well – an operator who does not have the appropriate training is not allowed to access particular tasks in the system. The quality teams are integrated and many tasks in the system require a quality engineer to either witness in process or post process and sign off tasks in the system.

- **Quality and compliance:** From my discussions, the FAA holds Company A to the standard that they will follow the quality system they designed. When the inspectors visit the floor, they tend to spend time asking MTs about the task including what procedure they are working to. If they determine the MTs are knowledgeable about the task and resources needed the FAA is confident

in the process. It is less important to the regulators that the MTs have their procedures and specs out and open while they are performing the task. In the case of Non Conformances (NCs), MTs and work teams are much more likely to attribute them to human error rather than blame the procedure/system. MTs and work teams are encouraged to self-report so that corrective action (e.g. training/rotation) can be provided as needed.

3.2 Nuclear (Company B)

At Company B, they adopt a three pronged approach to operator success.

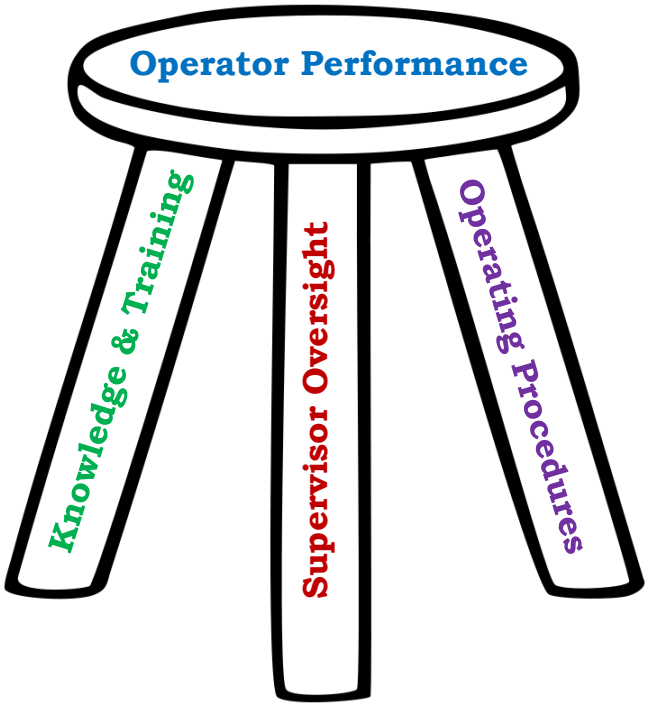


Figure 2: Three pronged approach to operator performance

At a high level, Company B has a balanced approach to each of the legs on this stool. They spend equal efforts on knowledge and training and supervisor oversight as they do on procedures. You cannot achieve high levels of performance without each of these legs. However, every organization pays different

amounts of attention to each component. One key takeaway from Company B is that a balanced approach is more sustainable and can yield better results.

- **Procedure content:** Procedures tend to contain information strictly related to the job at hand. Each line in the procedure names the equipment and the desired state for it to be in. Operators print out the latest procedure from their online system before going to the job site to start their shift. Details about how to perform specific tasks are not usually spelled out. Certain notes are highlighted indicating expected outcomes, critical steps or dangerous situations.

- **Procedure style:** All procedures are standard word documents. Separate visual aids are sometimes provided on the job location but a majority of instruction is provided through written text. This is primarily to enable 'placekeeping' (discussed later).

- **Procedure use:** Company B classifies procedure by type (normal, abnormal and emergency) and level of usage (continuous, periodic and reference).

    - *Normal:* These procedures are used most frequently. They provide instructions for how to perform tasks under normal operating conditions.
    - *Abnormal:* These procedures provide instruction on how to deal with abnormal situations. Process upsets, alarm conditions and most atypical situations are discussed.
    - *Emergency:* These procedures are for when the plant is in a state of emergency. Evacuation, reactor containment, and other emergency scenarios come into play.
    - *Continuous:* These procedures are intended to be followed in-line while executing a task.
    - *Periodic:* These procedures don't need to be followed continuously during execution but should be consulted periodically as indicated.

- *Reference:* These procedures do not have any requirements for in-line consultation but should be available for reference while performing the task.

Jobs are often performed in pairs with certain steps requiring either continuous or independent verification. While following the procedure, operators use a practice called placekeeping – circle the step at the start and slash at the end. Through placekeeping, operators ensure they follow through every step. It also is a quick visual indication that all steps have been completed at the end of a section.

- **Authorship:** A dedicated group of ex-operators is in charge of writing procedures for operations. This is quite different from Amgen where engineers write SOPs and writing SOPs is an ancillary responsibility. Engineers are included in the authorship process as needed as technical reviewers, but operators write the procedures how they would want them written. This allows for procedures that are execution focused and suited to the needs of the operators on the ground.

- **Training:** At Company B, there is a strong approach to training and qualification. To perform operations there are strict training requirements. Operators undergo training on a regular basis using on-site learning labs. This training not only covers how to perform certain tasks, but also how to use procedures effectively. At the same time, there are also training requirements to write, review and approve procedures at all levels. The Procedure Professionals Association (www.ppaweb.org) provides a working group for procedure standards, techniques and requirements. They also provide training and certification programs.

- **Commitments:** Procedures often get revised when there is a tech alert, regulatory requirement, or some key step that was missed. At Company B, all of these revisions are tracked in an online database and referenced by a tracking number in the procedure. This way, any modifications to procedures with a specific background can be tracked and managed. Any time anyone wants to

remove a line from a procedure, they need to ensure there are no outstanding commitments associated with that line. It also helps users understand the background behind certain requirements that are not inherently obvious. This is an effective way of not only preserving knowledge, but also the justification and history of any instruction in the procedure.

- **Supervisory oversight:** At Company B they put a strong focus on supervisor engagement. Supervisors hold toolbox talks at the start of every job, verbally going through important steps and safety considerations. Additionally supervisors take a strong role in watching operations when they can and providing immediate feedback on not just the outcomes but how they (the operators) achieve their outcomes.

3.3 Key Takeaways

In the above two sections, we detail out a number of the tools and techniques Company A and Company B use to enhance their procedures and improve human performance in their organizations. Not everything we learned from these two industries can be directly applied to biomanufacturing at Amgen, but below are the key takeaways:

- Operator performance is achieved by a balanced approach to procedures, training and supervision. This lines up well with Amgen's HRP program as well as the ABC method discussed in Chapter 2.
- Even older organizations can successfully adopt new technologies and adapt how they work. If there is real value to be gained, engineers and operators are willing to learn how to use new technologies.
- Streamlining procedures goes hand in hand with strengthening the training program and overall staff knowledge. The total amount of knowledge and control provided between the three avenues stays the same but the balance can (and should) adjust accordingly.

- Dedicated resources (with an appropriate background) assigned to writing procedures enables better procedures. Operators writing SOPs leads to SOPs being more execution focused and user friendly. Assigning dedicated ensure that enough attention is provided to SOP development and more importantly revisions.

The above points do not themselves, individually or in aggregate, offer a silver bullet to help Amgen improve SOPs and implement HRP. However, we take the lessons from above and together with the rest of our research are able to develop a proposal for a new system of SOPs.

4 Background

Originally coined by Hungarian agricultural engineer Karl Ereky, biotechnology refers to the practice of using technology to enable biological systems, living organisms or their derivatives to be converted into useful products. Founded in 1980, Amgen has been a leader in biotechnology developing, manufacturing and delivering lifesaving therapeutics to patients across the globe (Amgen, Inc.).

In this chapter, we will present a brief overview of Amgen, its organizational structure, followed by a more detailed discussion about manufacturing at Amgen.

4.1 Amgen Overview

Amgen Inc. – originally Applied Molecular Genetics – is a biotechnology company focused on developing large molecule therapeutics to help treat grievous illnesses. Amgen is a global biotechnology company with manufacturing locations in North America and Europe. Amgen makes a number of products targeting mainly areas of oncology, hematology and inflammation. Some notable products include Neupogen and Neulasta (treat infections in cancer patients); Enbrel (treats rheumatoid arthritis); and Aranesp and Epogen (treat anemia) (Amgen, Inc.).

Like other biotechnology and pharmaceutical companies, Amgen's products are the subject of an extensive review period (including trials) before the Federal Drug Administration (FDA) approves them for use. The FDA acts as the government's watchdog not only during the approvals process, but also for all development and manufacturing activities.

4.2 Organizational Structure

The organization chart below gives an overview of Amgen's organizational structure

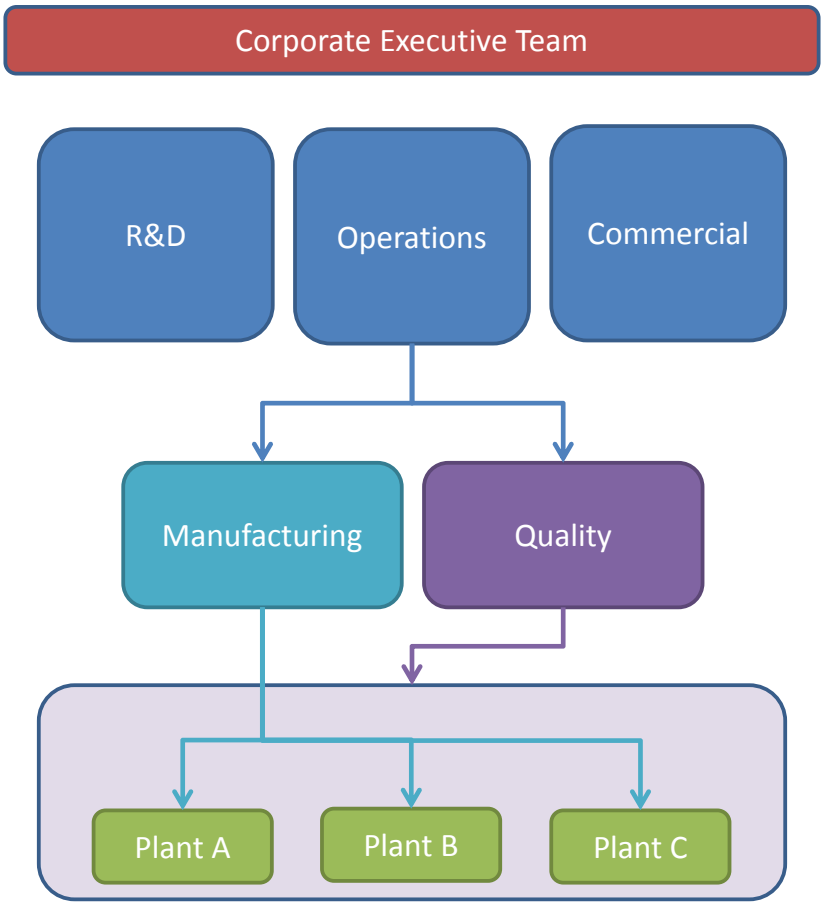


Figure 3: Organizational Structure of Amgen

As you can see from the chart above, Manufacturing and Quality both roll into Operations with representatives from each represented in plant management. This, in part, is to ensure that Quality is an independent observer and not beholden to manufacturing pressures. Each plant is allowed to operate fairly independently with no requirements to match most processes and procedures across facilities. Even facilities collocated with each other can have different procedures to accomplish similar goals. This allows individual plant managers and staff to adapt processes and procedures to suit their needs effectively. On the other hand, absence of centralized review results in some relearning and rework to occur since best practices are not easily discovered and communicated between plants. Plant management at each plant will follow the corporate guidance for HRP, but to different degrees and with their own personal adjustments. As a result, implementing standardized processes across the manufacturing network

is a challenge. Additionally, it is worth noting that Plant Managers are rewarded for plant level performance to encourage innovation and optimization of issues nascent to the plant. This is good because it encourages solutions that make sense in the local context. However, a plant focuses attitude does not encourage managers to put a lot of activity into initiatives which do not have immediate local results.

The manufacturing technologies group was in part developed to address this challenge and form the bridge between different plants at management and technical levels. The manufacturing technologies group acts as a linking group connecting plants across the manufacturing network through global projects and encouraging network thinking at management and technical levels. Given the goals of the project to influence SOPs and operations across all manufacturing sites, manufacturing technologies was selected as the group from where this project will be managed. Similar initiatives like the Purposeful Presence on the Floor (PPoF) and the Global Qualification program are also managed out of this group.

4.3 Manufacturing

Amgen has two types of manufacturing plants: clinical and commercial. Clinical plants manufacture products for drug trials while commercial plants manufacture products for commercial sale and distribution. Outside of the customers for their products, both types of plants have a very similar manufacturing process:

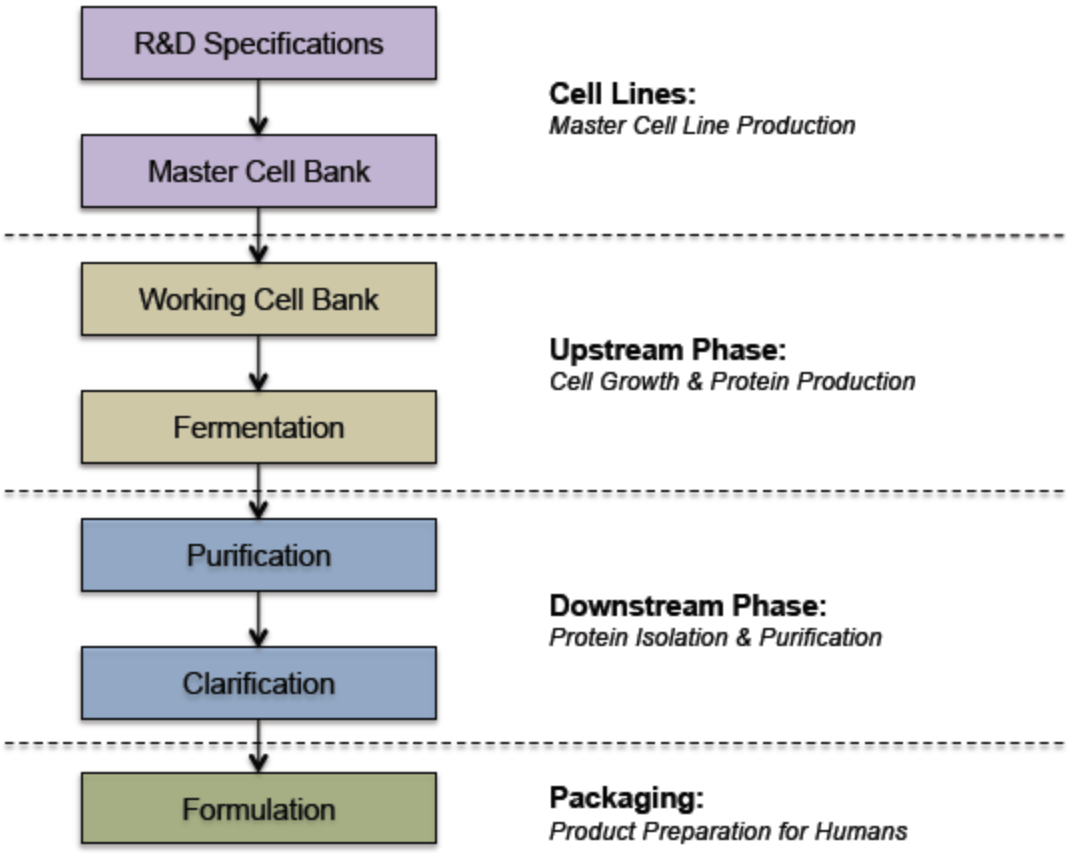


Figure 4: Manufacturing process at Amgen

Drug products are prepared in batches, with floor operators playing an important role in a semi-automated process. Technology has reduced the amount of manual labor required to manufacture product but it has far from eliminated it depending on the portion of the process. Lean principles are embraced on the floor and each team does their best to foster continuous improvement. Recently, iPads have proliferated in the manufacturing environment with most operators querying their procedures through an electronic database rather than printing out hard copies. Since viewing the procedure on the iPad is no different than viewing a paper copy of the procedure, this implementation has been named "paper on glass". Using the iPads allows operators to be able to call up multiple procedures without leaving the manufacturing area and allows for a neater working environment in absence of extra papers. The 'paper on glass' experience does little to mitigate the cumbersome nature of juggling references: the mental dexterity required is still the same even if the physical juggling of paper documents has been improved.

5 Project Motivation

The genesis of the project find its roots in Amgen's High Reliability Performance (HRP) initiative though concerns surrounding SOP compliance and ease of use have existed for some time prior.

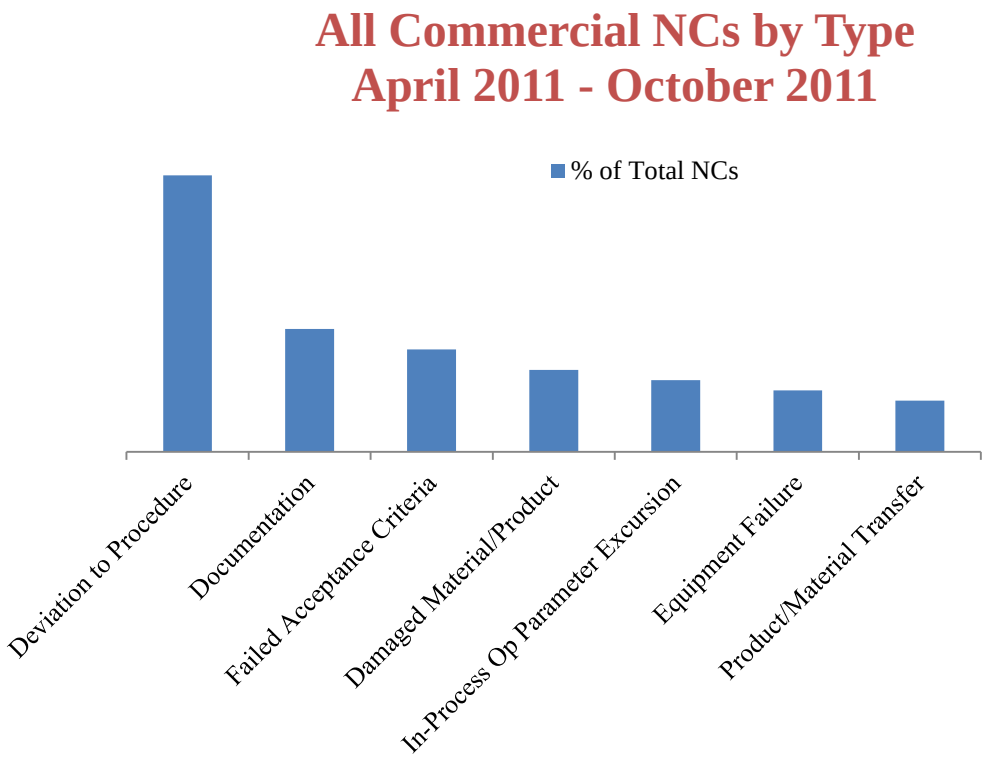


Figure 5: Distribution of Commercial NCs by root cause

The chart above shows root cause attributions for NCs from all commercial manufacturing locations. The root causes are attributed jointly by the manufacturing and quality staff on the floor with management approval. We see that 'Deviation to Procedure' and 'Documentation' form the bulk of the NC (non-conformances) issued in this time period. These NCs, coupled with associated losses in productivity, adversely impact our business and prevent us from achieving our quality and high reliability goals. These procedural deviations can also represent a significant compliance risk during regulatory inspections. The figure above shows us why we need to revitalize our SOPs and why NCs are one of the

primary drivers of this project. From our discussion about the A+B+C method in chapter 2, it is worth mentioning that there are three main reasons why we chose to focus this project on SOPs:

- Training and Supervision are being addressed through other initiatives at Amgen (GTQ and PPoF)
- The FDA has strict guidance around the adherence to SOPs and how they are intended to be used during operations. This puts an added focus on improving SOPs to improve operations overall.
- Staff (operators, engineers and management) who have had to use SOPs have voiced their concerns about the 'user friendliness' of the current SOPs.

In this chapter we will investigate all the factors described above.

5.1 SOPs in HRP

Amgen's HRP program relies strongly on Defense in Depth (DID) concepts. Defense in Depth was initially military strategy in which a strong defense against an attacker depended on creating multiple layers of independent or redundant defenses. Since then, this concept of multiple layers of defense has been applied to many nonmilitary situations, most notably nuclear safety. According to a report on Defense in Depth by the International Nuclear Safety Advisory Group (INSAG), "All safety activities, whether organizational, behavioral or equipment related, are subject to layers of overlapping provisions, so that if a failure should occur it would be compensated for or corrected without causing harm to individuals or the public at large. This idea of multiple levels of protection is the central feature of defense in depth..." In nuclear safety, DiD principles are applied to i) prevent unwanted events from occurring and ii) limiting the negative consequences of unwanted events that do occur. Layers of protection are built in to the system through equipment design, safety controls, maintenance and operating procedures, employee training, and management culture (INSAG, 1996). At Amgen, HRP is achieved by applying Defense in Depth concepts based on integration of 3 layers of operational control.

1. **Equipment Engineering:** This layer deals with designing reliable systems that have built in protections against many different kinds of risks. Through equipment engineering, we identify risks early in the design and leverage improved design requirements and standards to include mitigations to any risks detected. Any additional mitigation required through testing and surveillance is also identified.
2. **Standard Operating Procedures:** The next layer in DiD links equipment to people. SOPs should be appropriately designed to account for human factors. They should be well written and tested by experienced operators. SOPs should be execution focused while being cognizant of the knowledge being passed on by the equipment layer and the activities occurring in the staff training layer.
3. **Staff Qualification:** The last layer in DiD deals with staff training and qualification. The core message is that well trained staff stewarded by a robust qualification program is an excellent line of defense to potential deviations to process.

Aligning with these concepts of DiD, Amgen has initiated a number of programs such as:

- *The Global Qualification program* is redesigning the current training program at Amgen. Training based on learning modules with clear instructional goals is a core principle. These training modules are currently in development.
- *The Purposeful Presence on the Floor (PPoF)* initiative aims to incentivize and encourage management to engage with the manufacturing process and operating staff directly on the floor. Through this program, floor supervisors are provided a framework to engage with floor operators and operations on a more systematic basis. Supervisors get more involved in issues on the floor, employee training and operational improvement opportunities. This enables quick problem solving, immediate feedback and a culture of success. PPoF has been rolled out to most Amgen locations, though adherence tends to vary from site to site.

Yet we don't see an initiative addressing SOPs which are the centerpiece of the second layer of DiD. This internship project is proposed as a way to fill that gap. While there have been some efforts under the

DiD and HRP umbrella to improve procedures, they have been largely incremental. While this thesis does not fit exactly into the DiD rubric, the motivations for the project find their roots in this program.

5.2 Compliance concerns

According to Current Good Manufacturing Practice (CGMP) regulation from the Food and Drug Administration (FDA) [CFR 21, Section 211, Subpart F],

"*(a) There shall be written procedures for production and process control designed to assure that the drug products have the identity, strength, quality, and purity they purport or are represented to possess. Such procedures shall include all requirements in this subpart. These written procedures, including any changes, shall be drafted, reviewed, and approved by the appropriate organizational units and reviewed and approved by the quality control unit.*

(b) Written production and process control procedures shall be followed in the execution of the various production and process control functions and shall be documented at the time of performance. Any deviation from the written procedures shall be recorded and justified."

The FDA guidance is clear: operating procedures must be followed during execution of activities. Amgen adopts the most conservative stance on this issue and expects operators to follow their SOPs *while executing* manufacturing operations. SOPs must be out and be followed at *all* times. However, the reality on the manufacturing floor does not always meet expectations. During our investigations, we discovered that while we did not see any issue where the operator was not manufacturing to standard, many times it was difficult for the operator to follow the SOP *during* execution. While the difficulties with the SOPs themselves are reason enough to spur change (as discussed next), concerns surrounding compliance to Amgen's CGMP standards certainly provided significant incentive for this project.

5.3 User friendly procedures

Perhaps the most compelling motivation to change the current SOPs comes not from senior management or regulators, but from the operators using the SOPs on the manufacturing floor. While the current SOPs are adequate to get the job done, staff feedback indicates there is considerable room for improvement. This information was obtained through informal interviews with operators in both clinical and commercial manufacturing plants. When questioned, most operators readily admitted that many SOPs were difficult to follow. Experienced operators often alluded to the fact that they would often work from memory than try to decipher SOPs. While all operators indicated they wanted to see better SOPs, they did not necessarily have an idea of what better SOPs should look like. Some areas of concern the staff raised include:

- SOPs are too long/too much detail: The staff prefers not to have to parse through pages of text in order to find the few relevant pieces of information they need to perform their job. Complaints of this variety can indicate that our current SOPs are not focusing on providing the right content at the right level of detail.
- SOPs do not have the information needed: This complaint typically indicates either a) missing detail or b) inadequately presented information.
- SOPs have too many cross references: Given that current SOPs are typically written to cover a particular type of equipment, an operator trying to execute a particular job will need to reference multiple SOPs simultaneously to follow instructions and stay in compliance. This is both physically difficult to manage (multiple documents in a cramped space) and mentally taxing.

In a survey we gave to operators in one of the manufacturing plants, we queried them to see to what extent SOPs contribute to errors and non-conformances.

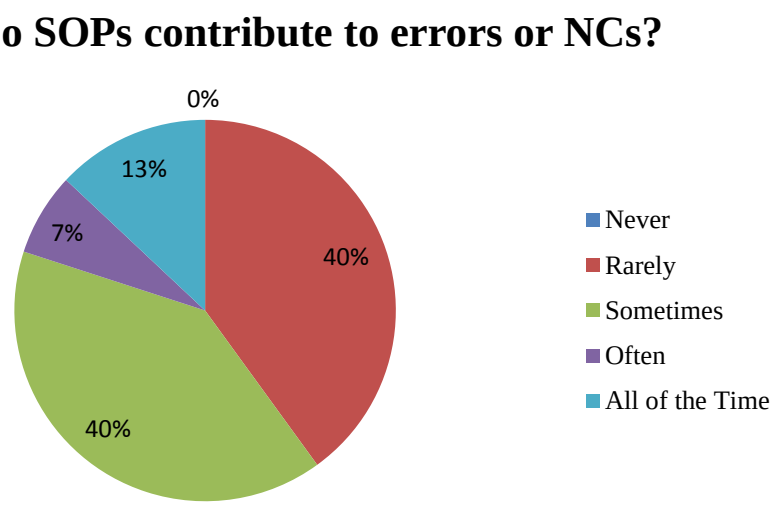


Figure 6: Operator feedback on SOP contribution to NCs

As we can see from the chart above, the operators on the floor recognize SOPs as a significant contributor towards errors and NCs. It important to note that these issues are not idle complaints from operators on the floor looking to make their life easier: each of these issues has real impacts on productivity, quality and compliance. Amgen's leadership recognized these issues as significant to operational success. Amgen's then SVP of Operations created a video in which he outlined the importance of following procedures for safe and compliant operations. This video was distributed to every staff member at Amgen. He then solicited the manufacturing technologies group to develop an approach that improved SOPs – specifically in manufacturing. This attention from senior management led to the creation of this internship project. The user centric approach of this project stems in a large part from the desire of Amgen's leadership to address human factors concerns with SOPs.

6 Current State Analysis

In this chapter we paint a picture of the current SOP ecosystem. This includes users, developers, the manufacturing plants, associated stakeholders and outside influences. This chapter will build on chapters 2 and 3 and provide a picture of how SOPs are developed and used today.

6.1 Operations on the floor

The primary purpose of Standard Operating Procedures is to provide instruction to operators on how to execute their tasks. Yet, at Amgen SOPs are not the only source of information and instruction for manufacturing staff. In order to understand SOPs, we must understand how information flows and is used during regular operations. To help explain this process, we will use a cooking analogy.

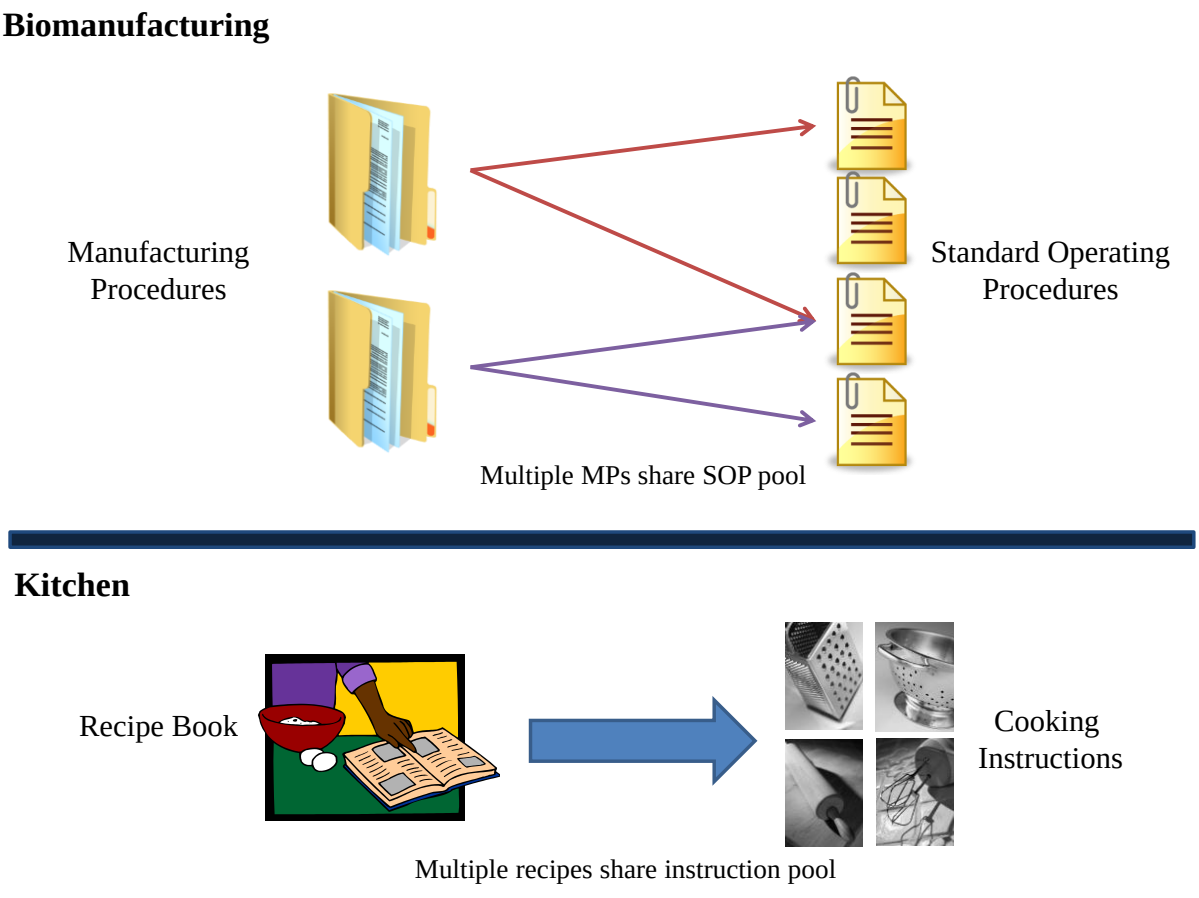


Figure 7: Relation between MPs and SOPs

6.1.1 The Recipe/Manufacturing Procedure

While cooking we have the option to make a number of different meals. We could make an omelet or bake a cake. Depending on what we decide to make, we need to select the appropriate recipe that tells how to combine the right ingredients to produce the desired meal. Similarly, when manufacturing a particular product, we use Manufacturing Procedures (MPs) to obtain preparation instructions. Every unique product has its own MP which tells the staff what ingredients need to be prepared in what fashion with which equipment to achieve a successful product yield. Though unlike cooking recipes, MPs form the basis of Batch Records (BRs) – a record of how each drug batch was prepared for FDA audit. Important data is recorded into the MP (weights, measures, temperatures, calibration information, etc.)

6.1.2 Cooking instructions/Standard Operating Procedures

Continuing with our cooking analogy, let us say the recipe calls for "three eggs, beaten". The recipe doesn't specify how we are supposed to beat the eggs or the best way to crack an egg. For this we turn to our egg beater manual and our 'eggs for beginners' handbook. In the context of biotech manufacturing, both the manual and handbook represent SOPs. SOPs provide instruction on how to execute each step of the MP where required. Currently, SOPs are equipment based: every possible kind of task we want to execute using a particular piece of equipment is all in one SOP. Therefore, to perform a task that requires multiple pieces of equipment we need to source the relevant sections of relevant SOPs – this is quite difficult to manage on the floor during live operations.

6.1.3 Using appliances/Automation feedback

Microwaves use an electronic interface to let us know when the food is ready and preset settings to make preparation of select dishes easy. The plant automation systems of computers, sensors and

PLCs, in a similar manner, communicate information about the process to the operators on the floor. The operators use this information to adjust how they perform manufacturing operations as needed in concert with guidance from MPs and SOPs.

6.1.4 Culinary School/Training and development

Before we are allowed to cook in a commercial kitchen, we need to undergo the required training at culinary school. Similarly, before we can execute operations on the manufacturing floor, we need to meet the requirements of a strict training program. The information provided in training is designed to give the operators the basic skills and knowledge they need to perform the job and respond to abnormal situations. Currently, Amgen uses SOPs to train operators in different knowledge and skill areas. Most operators come in with either two year or four year degrees. Many operators are hired straight from school though there are a number of experienced hires as well from other biotech and pharmaceutical companies. Through the onboarding process, all operators are provided formal training through a combination of instruction and tested self-study requirements. SOPs are used to provide some of both. Additionally, a lot of training is conducted informally on the floor by experienced operators – a kind of apprenticeship. Here as well, SOPs are used as a teaching aid and guide.

6.1.5 Supervision on the floor

In any commercial kitchen, there is a head chef who supervises the rest of the cooks who are engaged in preparing the food. They provide oversight and advice, and look for ways to improve the overall performance of the team. On the manufacturing floor, that role belongs to the floor supervisor. Operators get feedback and other useful information from management that factors into how they execute their job in concert with all the other sources of information previously described.

Through a simple cooking analogy, we have explained the complex flow of information on the manufacturing floor. SOPs are a critical source of information for operators but they work in concert with other sources. We are looking to improve SOPs to improve human performance, but SOPs do not exist in isolation. Any improvements to SOPs will need to be made cognizant of the other components in its ecosystem. In the next sections we discuss the structure of SOPs, the relations SOPs have to other system components and external factors.

6.2 Structure of SOPs

SOPs have the following structural characteristics:

- **Text based:** most SOPs are word documents consisting primarily of bulleted prose with very little visual information.
- **Equipment based:** they cover all tasks as related to a particular piece of equipment.
- **Reference heavy:** most SOPs have a long list of references to other SOPs. Usually operators cannot perform a complete task without referencing more than one SOP.
- **Overlapping information with training:** since SOPs are often used for training, they often contain types of information not directly relevant with task execution (background information, roles and responsibilities, troubleshooting guides, etc.)

6.3 Interaction with training and qualification programs

Currently SOPs serve the dual purpose of being the tool to provide training and qualification in addition to being the instruction set on the floor. By attempting to be the tool for both these competing priorities current SOPs end up not completely meeting requirements for either job. This requirement forces SOPs to be quite lengthy since not only do they have to cover execution details but they also have

to cover basic concepts, background information and other kinds of information normally covered in training.

6.4 Interaction with operators

The expectation from Amgen and Good Manufacturing Practice (GMP) is that the SOPs are out and followed while operators are performing a task. This requirement turns out to be difficult to both meet and enforce in practice. To meet this requirement, operators would have to read every SOP and every reference SOP for each task - this is cumbersome for most tasks of medium complexity and beyond. Most manufacturing teams realize it is difficult to perform tasks while juggling multiple stacks of paper at the same time. Instead, most operators reference only select sections based on their level of experience and comfort with the task at hand. Often, the trouble is not too much detail but too little detail. Some knowledge is not explicitly documented but is provided through mentorship and on the job training. For example, it is common for inexperienced operators to shadow/support experienced operators till the shift lead feels comfortable they are able to work on their own. This is particularly important for knowledge not captured directly in SOPs (e.g. locations of key chemicals in the particular cell). We often noticed operators working in pairs where the senior operator would explain the background and precautions before starting a particular job. Other knowledge is available in SOPs but not in the format that suits the job (e.g. written text to describe mechanical assemblies). In short, while operators continue to execute their tasks safely, it is difficult for operators to meet the standards set by GMP for following all SOPs in line with execution.

6.5 Interaction with Quality

As mentioned before, SOPs are attributed as the root cause for a significant number of non-conformances (NCs) in manufacturing. Our research indicates that this is not necessarily because SOPs

themselves are ripe with deficiencies, but rather that they represent an easy way to close out NCs. Per Amgen's quality process, NCs, once identified, have to be closed out in a specific time period. At this juncture, two cultural factors come into play:

- There is tremendous pressure within the organization to close NCs as quickly as possible.
- There is a reluctance to assign personal responsibility for an NC to any particular party in the organization.

Considering that root cause investigations often yield inconclusive results and SOPs are easy to modify, SOPs are the best target for a root cause investigation. It becomes easy to close out NCs with SOPs as the root cause since all that is typically required is some additional language in the SOP. If this happens enough, it leads SOPs being bloated with verbiage to cover all kinds of situations and topics not intended by the original author or in some cases even desired by the audience. Yes, there are certainly cases where SOPs are the root cause leading to an NC. However, our research indicates this tendency for NCs to be ascribed to SOPs does exist and might even contribute to creating poorly designed and cumbersome SOPs that lead to legitimate NCs down the road.

If there were a dedicated group of authors, in charge of maintaining and developing new SOPs, it would be considerably more difficult to modify SOPs without justification much less assign them as the root cause for a NC. Yet no such dedicated group of authors exists and it is quite easy for modifications to a SOP to get approval. Most SOPs are written by engineers as a secondary responsibility. Without dedicated authors, there is no one to defend the content of the SOP.

None of our research indicates that any operations are occurring outside of the standards set by quality or that the product itself is under any major risk. Yet the issues described in this section present real cultural and management challenges to Amgen becoming a HRP organization.

7 Future State Proposal

In this chapter, we introduce our new vision for SOPs. This includes a new approach to SOP development and use as well as a portfolio of SOP options depending on the task at hand. We begin by explaining our goals and objectives followed by the guiding principles of our new approach. Following that, we will go into details about our portfolio of SOP options and how to select the appropriate option given the needs of the user and the task at hand. Lastly, we will discuss how this new vision will impact surrounding systems and stakeholders.

7.1 Goals and objectives

We aim to create a new SOP system to provide meaningful procedures to our operators. With this new system, we will accomplish the following goals:

- Procedures will be developed to suit the task at hand in terms of content and format.
- Procedures will be clear and concise.
- Procedures will incorporate elements to prevent error and ensure safety and quality.
- Operators will be able to access different levels of information with ease – procedures, reference documents, training guides, etc.
- Expectations around procedure use and compliance for each task will be clear and established.
- Management and staff share a joint responsibility for ensuring procedures are effective and current.

Coupled with the goals above, we strive to improve productivity, quality, and safety performance in our operations. We desire to move towards a culture that insists on 100% compliance and use of established procedures.

7.2 Guiding principles

As we consider an alternative SOP system, these are the guiding principles that serve as the foundation for our approach:

- **The Operator is our primary audience:** All procedures will be designed to enable the operators to *perform their job* in best way possible. By focusing on the job at hand, we want to make our procedures task based. Information that is not procedurally directed on the task at hand will not be in the procedure. This includes engineering content, background information, and other reference topics. Information related to managing work or overall process is not task-based and will be handled separately from procedures.

- **Procedures will be concise and clear:** The procedure will contain the exact amount of information needed to perform the job (no more, no less). The expectations for performing the job and the desired outcome will be indicated clearly.

- **Procedures will be task based (not equipment based):** One SOP will cover one task to simplify information communication and processing.

- **No more juggling references:** Procedures should not require multiple references and movement between numerous interfaces *on the part of the operator*.

- **Information hierarchy:** Information removed from current SOPs will be remapped to other repositories. These could be system descriptions, reference guides or even training materials.

- **Procedures are not a training substitute:** We expect our operators to be fully trained for the job they are performing. Work instructions are intended to be aids not crutches. Reasonable expertise on the part of the user is understood when crafting the procedure.

- **Instructions will be easy to absorb and comprehend:** While procedures are not a substitute for training, at the same time they should be crafted to provide information in the easiest manner to comprehend. This especially includes more emphasis on visuals with text playing a supporting role. Specific knowledge and terminology should not be a barrier to comprehension of the instructions.

- **Style will depend on the job:** Procedural format may be a picture, series of pictures, checklists or maps. The presentation of the information will be chosen to maximize the benefit to the operator in the context of the operation performed.

- **Controlled authorship:** Authorship of procedures will be controlled among a select group of subject matter experts (SMEs) and technical writers. These SMEs should include current experienced operators or staff with floor operations experience. This way, the content and style of procedures can be managed to standard. Once in steady state, procedures should not require frequent revision. This is also predicated on the idea that future procedures will be much leaner.

- **Compliance matters:** Even though effectiveness and ease of use for the operator is the primary goal, compliance is still an important goal and consideration. Key compliance requirements will be identified and met. An information hierarchy will be established to provide guidance on information use and expectations (i.e. standard procedure, reference document, troubleshooting guide, etc.)

The principles outlined above do not directly align with the aerospace or nuclear models, but take certain elements from both. The aerospace model is heavily outcome based with a large emphasis on training. Given the sensitive nature of the biomanufacturing process combined with a younger process and workforce, we are not comfortable relying solely on training and are compelled to provide more guidance in our SOPs. Our process focus lines up well with the nuclear model however we don't necessarily differentiate between different situations (normal, emergency, problem, etc.). We do create different spaces for regular operations information that goes into SOPs and troubleshooting information that could go into a different kind of document. We are focusing creating secure boundaries for standard operating procedures first. Troubleshooting instructions (or problem instructions as the nuclear model says) belong in a different vehicle separate from SOPs. Nomenclature around SOPs is important for complying with FDA guidance and therefore we cannot create multiple 'SOPs' for different situations. But like in the nuclear model, we propose different avenues for different kinds of information.

It is worth bringing up Perrow's point that not all tasks can be proceduralized. Specifically, he highlights the number of exceptions to normality and the amount of research needed to determine a path forward. In our new framework, tasks not readily proceduralized will have additional requirements for training and supervision. Per the A+B+C model, when one aspect cannot meet all requirements, the other aspects compensate. The degree to which we combine supervision, procedures and training for a given task is heavily dependent on operator input. Portions of the task that can be communicated effectively through procedure will and the rest will be managed through additional training and supervision.

7.3 Rethinking SOP Structure

Taking the goals and guiding principles from above, below we describe a vision for how individual SOPs can be designed from content as well as a style perspective. Once we explained our content and style approach, we go into details of example types of new SOPs followed by a discussion about what kinds of task each kind of SOP might be best suited for.

7.3.1 Content

Keeping with our principle to put the user/operator at the center of attention for SOP design, our research led us to identify the following types of information that are most important to operators in SOPs. The information below was obtained by talking to operators in multiple manufacturing facilities about which parts of the current SOPs they refer to the most and thus find the most valuable:

- **Execution instructions:** Operators are most concerned with how to perform the task at hand without errors. At the same time, they do not need simple steps that they know from training repeated in great detail. Operators want clear and concise instructions that leave little to the imagination.
- **Technical details:** There are certain numbers and settings that operators need to perform their tasks that should be provided. The technical information also needs to be provided in the appropriate context so that it is not misapplied during operations.
- **Detailed instructions for complex tasks:** The more complex or critical the task, the more information that needs to be provided to ensure that the steps to perform the operation safely are as clear as possible. Key safety considerations and areas where cooperation with other operators is required should be called out appropriately. The degree of detail should be proportional to the complexity and criticality of the task at hand.

Given the above information will be the focus of our new SOPs, the categories of information below will not be featured:

- **Background information:** Operators do not need to be presented with background information every time they execute an operation. This information, while appropriate for training to cover, does not hold the same degree of importance for day-to-day operations that a SOP is designed to cover.

- **Roles and responsibilities:** This is also an area that is appropriate to cover in training but does not require daily reiteration for most tasks.
- **Nonstandard operations:** Information related to troubleshooting, maintenance and other atypical scenarios does not belong in a *standard* operating procedure. This information is very valuable and should be available to operators should they encounter a nonstandard scenario but does not require revisiting each time operators execute normal operations.
- **Recommendations:** SOPs contain instructions, not recommendations. There should be no ambiguity in the mind of the operator as they read the SOP as to the path forward for successful operations. If a step is worth performing in a particular way in the spirit of HRP it should be an instruction not a recommendation.

The above discussion surrounding what does and does not belong in a SOP is driven by our user centric approach to design: what the operator needs stays in, and what they do not need does not. This implies that seasoned operators need to be involved at all key steps of the procedure development process. Their knowledge and preferences will have a big impact on the final content that goes into the SOP. Our new approach to content streamlines it to make it clear and concise. Complexity appropriate detail is another key consideration. In the next section, we apply similar principles to how the information is presented/communicated to the operator.

7.3.2 Style

When it comes to people and organizations learning and executing based on provided information, how the information is communicated (style) is as important as the information itself (content). Excellent information communicated poorly has zero impact on human performance. Current SOPs are stylistically identical: text based instruction reports with a combination of bullets and prose supplemented with a few pictures and illustrations. In our new approach, SOP style will depend on the needs of the user and the

nature of the job at hand. Below we examine just a few ways humans can receive information and instructions:

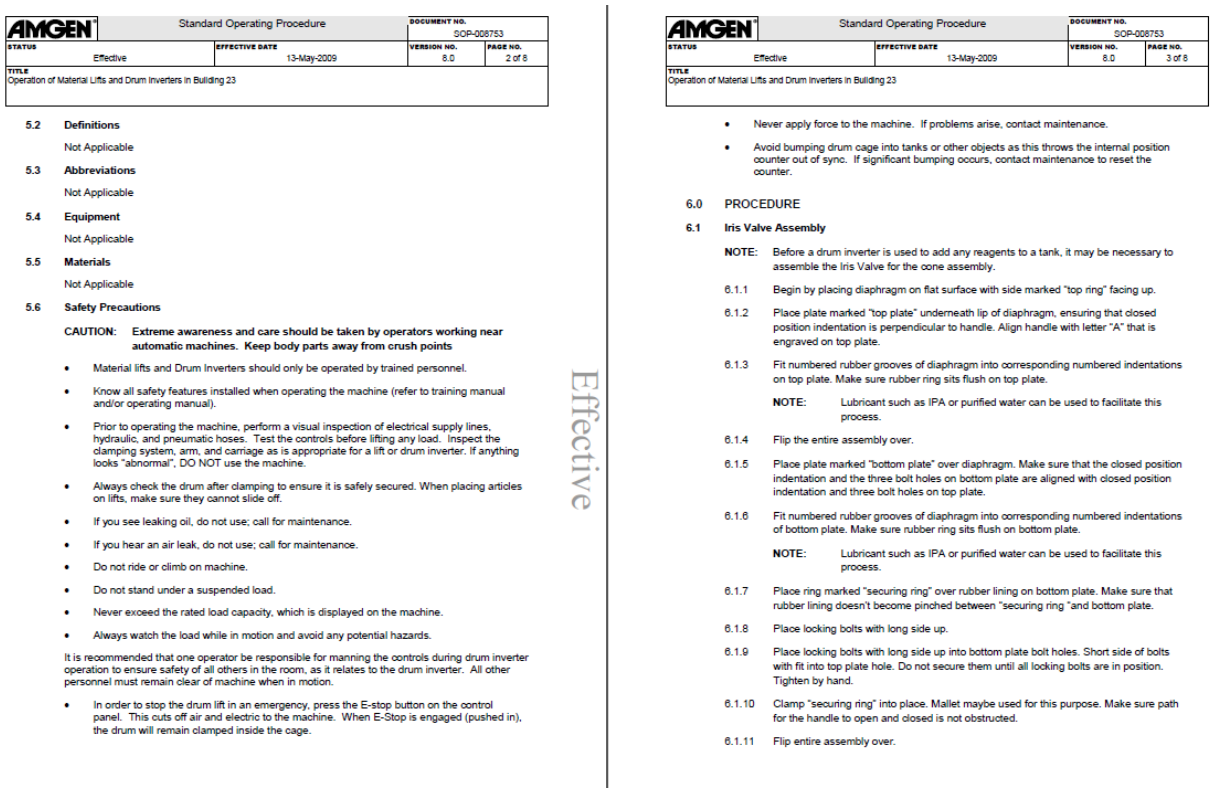
- **Written text:** the most traditional way to provide information in a manufacturing environment
- **Pictures and illustrations:** Some things (like mechanical assemblies) are just easier to communicate through pictures and illustrations. Context and perspective are communicated more effectively than through text. In terms of page space, visuals can often reduce the length of otherwise lengthy SOPs.
- **Audio:** An effective way to communicate information if hands and eyes are otherwise unable to access information because they are busy with task execution.
- **Video and animation:** Video works well at showing how an operation could be performed in the appropriate fashion. Video works particularly well for tasks that are performed very infrequently and operator familiarity is an issue.
- **Interactive media:** Instead of providing the complete information in bulk, oftentimes an operator would prefer to interact with the information based on job specifics and queries leading to a more intuitive working experience.

The above are just a few examples of the different ways an operator can receive instructions for their operations. SOP style not only controls how an operator receives information (an illustration versus a written description) but also how it is used. For example, an interactive procedure could not only control the rate at which instructions are provided but also how much information is displayed based on predetermined inputs.

In the next section, we will present some examples of new SOP types that are consistent with our new direction on content and style.

7.4 The SOP portfolio

As discussed in previous chapters, all current Amgen SOPs are presented in written report format. An example of a current Amgen SOP is shown below.



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TITLE: Operation of Material Lifts and Drum Inverters in Building 23

5.2 Definitions

Not Applicable

5.3 Abbreviations

Not Applicable

5.4 Equipment

Not Applicable

5.5 Materials

Not Applicable

5.6 Safety Precautions

CAUTION: Extreme awareness and care should be taken by operators working near automatic machines. Keep body parts away from crush points

- Material lifts and Drum Inverters should only be operated by trained personnel.
- Know all safety features installed when operating the machine (refer to training manual and/or operating manual).
- Prior to operating the machine, perform a visual inspection of electrical supply lines, hydraulic, and pneumatic hoses. Test the controls before lifting any load. Inspect the clamping system, arm, and carriage as is appropriate for a lift or drum inverter. If anything looks "abnormal", DO NOT use the machine.
- Always check the drum after clamping to ensure it is safely secured. When placing articles on lifts, make sure they cannot slide off.
- If you see leaking oil, do not use; call for maintenance.
- If you hear an air leak, do not use; call for maintenance.
- Do not ride or climb on machine.
- Do not stand under a suspended load.
- Never exceed the rated load capacity, which is displayed on the machine.
- Always watch the load while in motion and avoid any potential hazards.

It is recommended that one operator be responsible for manning the controls during drum inverter operation to ensure safety of all others in the room, as it relates to the drum inverter. All other personnel must remain clear of machine when in motion.

- In order to stop the drum lift in an emergency, press the E-stop button on the control panel. This cuts off air and electric to the machine. When E-Stop is engaged (pushed in), the drum will remain clamped inside the cage.

Effective

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- Never apply force to the machine. If problems arise, contact maintenance.
- Avoid bumping drum cage into tanks or other objects as this throws the internal position counter out of sync. If significant bumping occurs, contact maintenance to reset the counter.

6.0 PROCEDURE

6.1 Iris Valve Assembly

NOTE: Before a drum inverter is used to add any reagents to a tank, it may be necessary to assemble the Iris Valve for the cone assembly.

6.1.1 Begin by placing diaphragm on flat surface with side marked "top ring" facing up.

6.1.2 Place plate marked "top plate" underneath lip of diaphragm, ensuring that closed position indentation is perpendicular to handle. Align handle with letter "A" that is engraved on top plate.

6.1.3 Fit numbered rubber grooves of diaphragm into corresponding numbered indentations on top plate. Make sure rubber ring sits flush on top plate.

NOTE: Lubricant such as IPA or purified water can be used to facilitate this process.

6.1.4 Flip the entire assembly over.

6.1.5 Place plate marked "bottom plate" over diaphragm. Make sure that the closed position indentation and the three bolt holes on bottom plate are aligned with closed position indentation and three bolt holes on top plate.

6.1.6 Fit numbered rubber grooves of diaphragm into corresponding numbered indentations of bottom plate. Make sure rubber ring sits flush on bottom plate.

NOTE: Lubricant such as IPA or purified water can be used to facilitate this process.

6.1.7 Place ring marked "securing ring" over rubber lining on bottom plate. Make sure that rubber lining doesn't become pinched between "securing ring "and bottom plate.

6.1.8 Place locking bolts with long side up.

6.1.9 Place locking bolts with long side up into bottom plate bolt holes. Short side of bolts with fit into top plate hole. Do not secure them until all locking bolts are in position. Tighten by hand.

6.1.10 Clamp "securing ring" into place. Mallet maybe used for this purpose. Make sure path for the handle to open and closed is not obstructed.

6.1.11 Flip entire assembly over.

Figure 8: Example Amgen SOP

Note that the example format presented above is the consistent across all applications. In this chapter, we will present three new alternatives to the format presented above.

For our initial proposal we are offering three different kinds of new SOPs: instruction, diagram and electronic. Each different option is driven by a particular style of information presentation and can be easily adapted to the needs of the job and user. From a content perspective, they are all aligned on providing clear and concise instructions at a complexity appropriate level of detail.

7.4.1 Instruction SOP

Instruction SOPs are primarily intended for straightforward tasks with a few important technical settings and perhaps guidance on how to operate a particular piece of equipment or interact with its machine interface. An example SOP structure is illustrated below.

POF Pilot Procedure Conductivity Calibration SOP 008882

Setup per picture below

Sample Range (µS/cm)	Reference Solution
0–1,000	Any conductivity reference solution within this range: • Potassium Chloride Reference Solution D at 146.9 µS/cm
1,000–10,000	Any conductivity reference solution used within this range: • Potassium Chloride Reference Solution C at 1409 µS/cm
10,000–230,000	Any conductivity reference used within this range: • Potassium Chloride Reference Solution B at 12,856 µS/cm or • Potassium Chloride Reference Solution A at 111,342 µS/cm

Standardize

1. Select standard per table above. Standard should be at 25 ± 1C.
2. Rinse probe with purified water.
3. Press Tref. Set to no temperature reference.
4. Press Cell 2 times.
5. When indicated, dip the conductivity cell into standard. Press √.
6. After stabilization, read the value on the display. If the value matches the standard value press √. Else repeat.
7. If value of display doesn't match standard value. Adjust conductivity by pressing arrow keys.

Figure 9: Instruction SOP

In general, the template of the instruction SOP is:

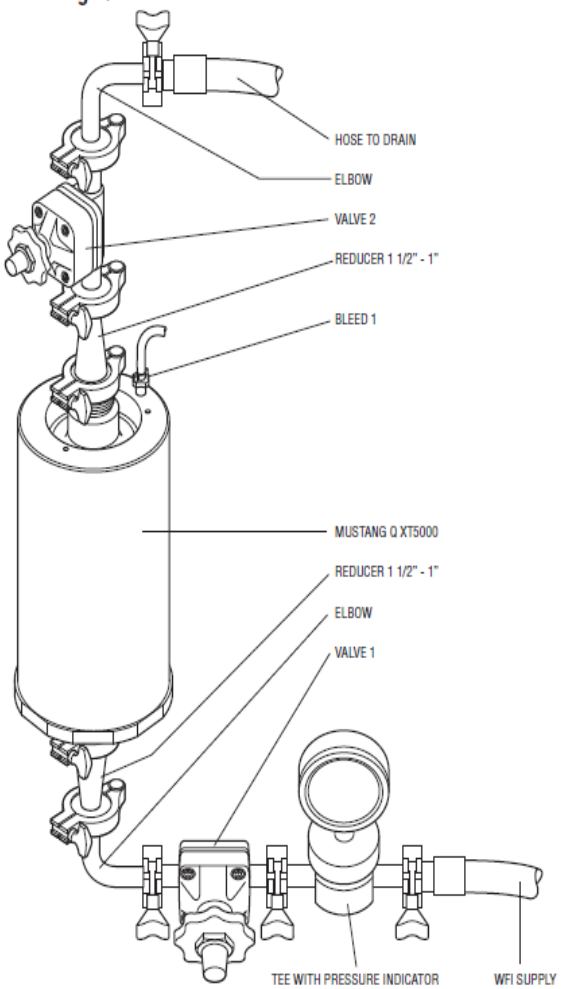
1. Present a picture of the equipment in its work context to provide perspective for the task
2. Detail out any key technical information needed to perform the particular task
3. Specify instructions on how to perform the task appropriately

The instruction SOP provides a simple framework to communicate instructions to operators for straightforward tasks.

7.4.2 Diagram SOP

The diagram SOP is best suited for those jobs where a visual mode of communicating information works best. Mechanical tasks, equipment setups and other similar operations would benefit from a diagram SOP where the picture or illustration is the focus and text plays an important supporting role. Examples of diagram SOPs are below.

Mustang Q



1. Close Valve 2.
2. Open Valve 1.
3. Slowly open WFI Drop (Do not open all the way).
4. Open Bleed Valve and Prime the Filter.
5. Close Bleed 1.
6. Slowly open Valve 2.
7. Adjust Valve 1 and WFI Drop to reach desired inlet pressure and outlet flow rate for the desired time. See table below.
8. Close WFI drop.
9. Disconnect all connections.

Filter Material/Item#	Inlet Pressure	Min. Time of Flushing	Flow Rate L/min
Mustang Q XT5000 (30000084)	5 ±1 psig at Ambient °C	13 minutes	8 - 10

Figure 10: Diagram SOP with illustrations

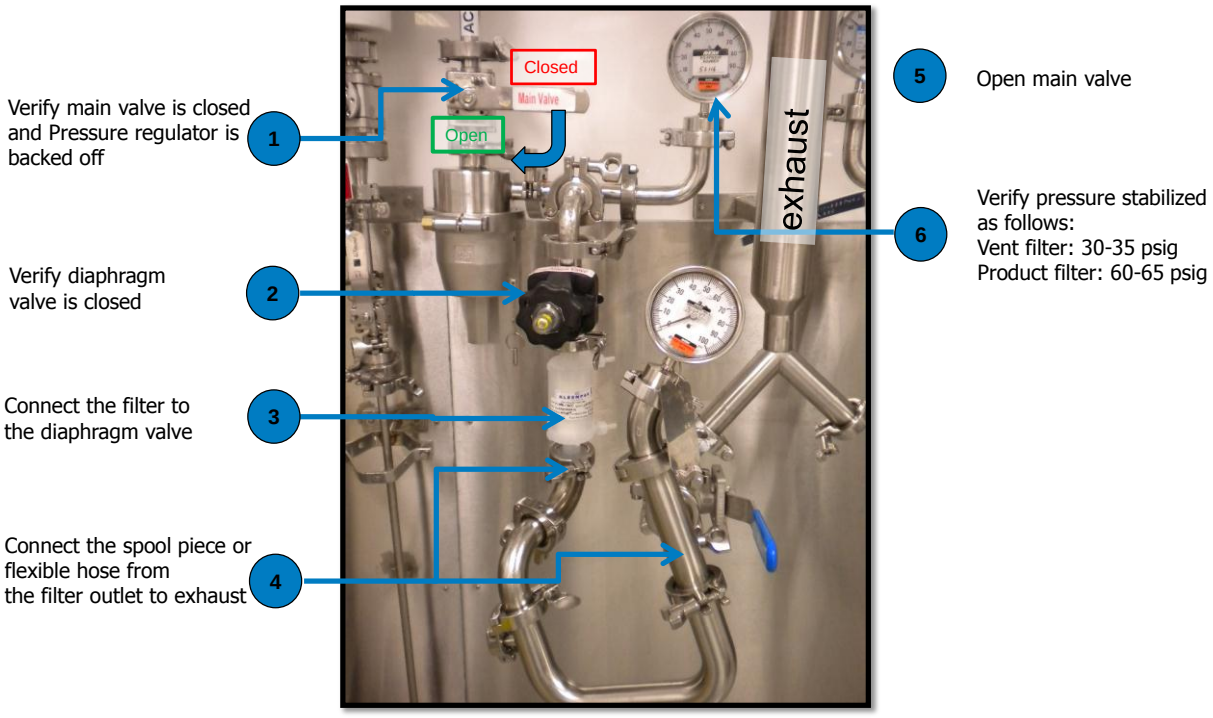


Figure 11: Diagram SOP with photograph

As can be seen from the two examples, there is no single way to approach the diagram SOP. The key highlight is that the picture the main focus.

7.4.3 Electronic SOP

Electronic SOPs represent boundless possibilities. Since technology allows us to easily manipulate how we present information, electronic SOPs could very easily mimic the experience with instruction and diagram SOPs. However, for the purposes of our project, electronic SOPs represent interactive SOPs. In an electronic SOP, the operator interacts with a computer to receive certain instructions. Based on the inputs from the operator, the computer determines (through predefined logic) the appropriate information to provide at a given time. Additionally, that information can presented in multiple forms (picture, text, and video) since the electronic medium is flexible to these requirements. An example of the home screen of one kind of interactive procedure is shown below.

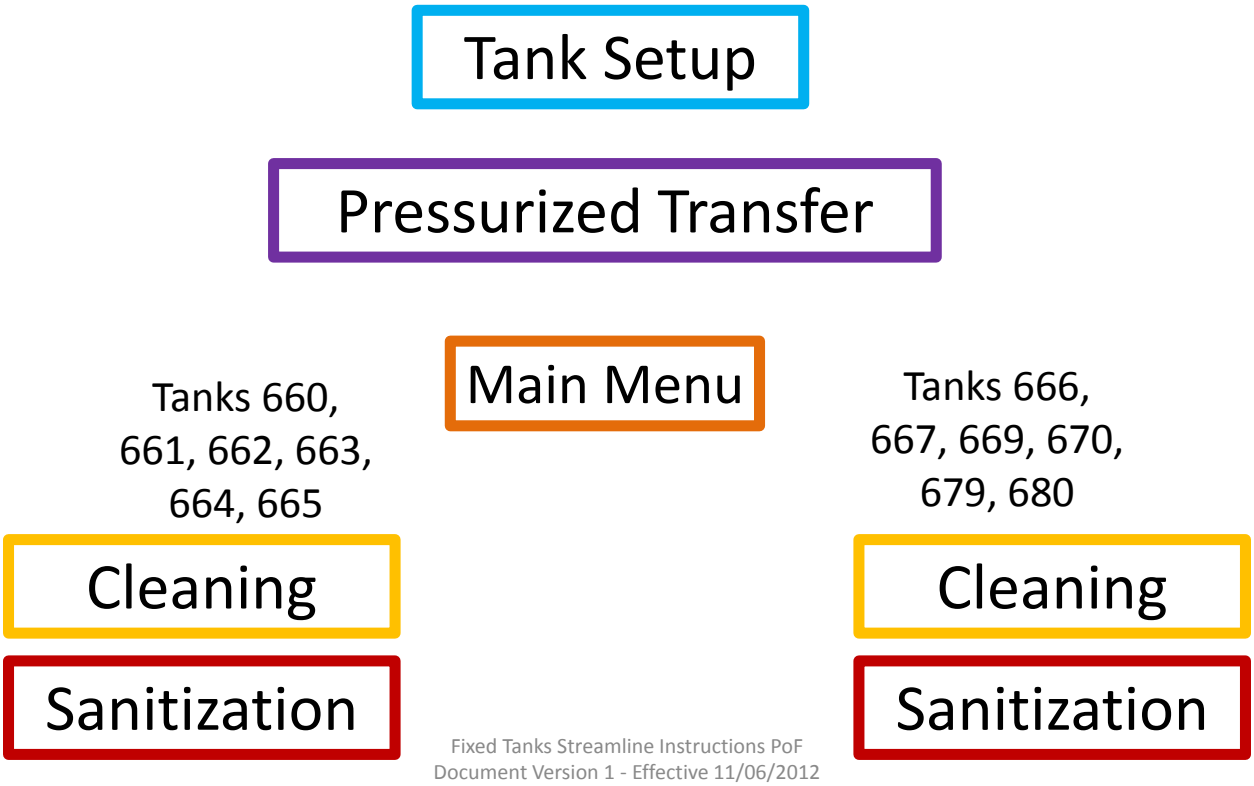


Figure 12: Navigation home page of electronic procedure

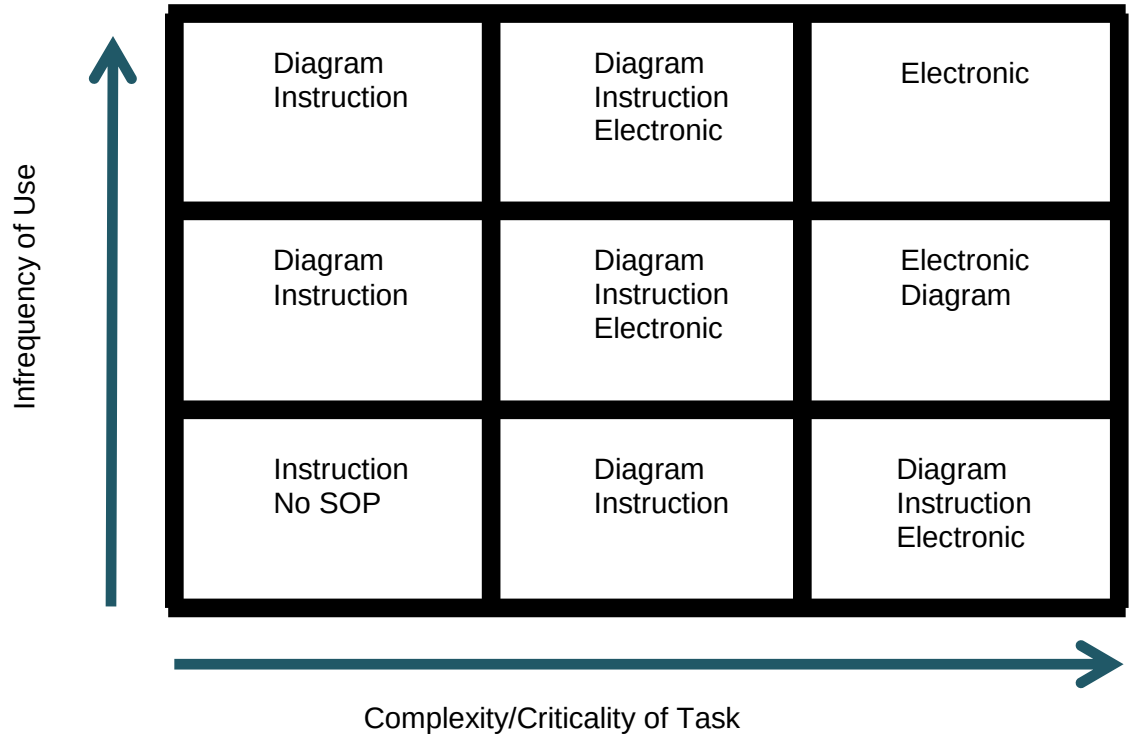
Above we have an electronic procedure prototype we developed for our pilot project (discussed later). We can see how different links allow the operator to navigate to different sections of the procedure. The electronic medium offers tremendous potential of how we provide instructions to our operators to maximize productivity and quality. The technical considerations around adopting new technologies to support this vision are discussed in a later section. Additional views of the electronic procedure we developed can be found in the Appendix.

The process of converting traditional SOPs to new SOPs like the ones described requires understanding in detail the needs of the operator for the task and what information is critical to

operational success. In the next section we discuss how to determine for what kinds of tasks which kind of SOP is appropriate.

7.5 Levels of complexity

The type of procedures used will depend on the task at hand: its complexity and criticality. Complexity of task includes multiple factors such as risk, number of operators required, frequency of task, etc. Criticality relates to how the task influences product quality and patient safety. This section discusses approaches to procedures for three different levels of task complexity/criticality. A simplified decision matrix to select procedure style based on these attributes is shown below as an example. We chose to use frequency and complexity as decision variables because those were the two considerations operators tended to bring up when discussing how they view and use particular SOPs. For example, we often heard that operators would often refer to even minor details of SOPs they did not use often or that were considerably complex. By using frequency and complexity, we made it easier to transition our new way of thinking into an existing mental framework.



Low complexity: These are jobs that are simple for most operators. They are typically routine, non-process related tasks that do not require specific qualification. Gowning or cleaning of parts could fit into this category. Currently, staff performing these tasks do not require this type of procedures to be open during use *most* of the time. Yet, performance of these tasks could be improved by simple SOPs with a few key instructions and details. For example, a diagram of someone with the correct gowning could be posted as a visual verification for employees in the gowning area. A picture showing the standard loading configuration for the parts washer (with the key settings labeled) could be placed right above the washer in the cleaning area. These would serve as replacement for the current text based SOPs.

Medium complexity: There are some jobs which are not routine and are not intensely complex. In these jobs, the operator will usually have the procedure nearby for reference if not open with them as they perform the job. However, long drawn out instructions tend to be overkill for non-critical jobs like transmitter calibration or buffer preparation. In these situations, either instruction or diagram procedures would be appropriate.

High complexity: Many of our processes have procedures that are highly complex due to the intricate nature of the tasks involved (e.g. bioreactor, chromatography, line set-up). Multiple steps, multiple operators, extended decision trees and numerous references are standard for these tasks. Most operators have their procedures open at all times while performing these jobs – which is good, though the cumbersome nature of the procedures makes the operations error prone and inefficient. In these jobs, an electronic application to guide the operator through the relevant steps would be appropriate. Multiple screens can guide the operator through each step, eliminating their exposure to information irrelevant to the job. This will allow the operator to focus on the task at hand and improve quality and effectiveness. Multiple scenarios can be built into the application to provide one simple interface to the operator without

having them consult 15 different documents and guides. Video demonstrations can also be included in this electronic format. In other areas, approaches like reader-doer can also be explored.

In this section we have outlined the different levels of complexity of different tasks and how an organization would approach choosing the appropriate kind of SOP to fit the needs of that task and the operator in charge. Our new vision is based on giving the organization a framework to use in which they can analyze the needs of the task at hand and use the framework to build custom SOPs based on the foundational templates presented (instruction, diagram and electronic). In the next section we discuss external interfaces to the SOP system and what these new changes mean for them.

7.6 External interfaces

7.6.1 Training

Everything we are proposing with regards to procedures is predicated on a strong training program. In the future state, SOPs will be decoupled from training materials. Training materials will be developed specifically to address the goals and information that the training program has. We expect all operators to be trained for the job they are performing. This assumption allows us to simplify the procedures to eliminate information related to foundational skills and knowledge. Much of the information that is in current SOPs might move into training materials. We don't expect the operator to know *everything;* however we do need to assume a certain proficiency to simplify the procedures. Procedures will be targeted to meet the needs of the least experienced fully qualified operator. The goal of the SOP is to provide that next layer of knowledge on top of the foundation provided by training. The SOP provides the additional info relevant to the job at hand and ensures consistent application and performance. Through the course of this project, we worked with the teams looking at revamping the training system through the Global Qualification Program to ensure we were on the same page. Though

currently Amgen does not have the training system we need to make this project successful in the long run, the progress of the Global Qualification Program towards the principles outlined above puts us on the right path. As a result, in the future state, SOPs and training programs will be developed in concert.

7.6.2 Quality and compliance

Quality is paramount and SOPs are a way to improve quality and reliability (see Chapter 5). Our new proposal should improve quality by reinforcing key messages and data, enhancing consistency and bring a better emphasis to quality control over quality assurance. Easier SOPs are not only easier to follow but are also easier to check against. This improves the performance of verification steps by Quality Assurance (QA) personnel. Compliance is a key consideration for SOPs and often compliance concerns can overwhelm the SOP development process. In a quest to close out NCs SOPs are seen as a way to show action has been taken. We need to move to a culture where we can distinguish between procedure deficiencies versus other issues.

In our new vision, the FDA is an important partner. It is imperative that they are informed and have the opportunity to ask questions about the new philosophy. New kinds of procedures may invite additional scrutiny and the FDA is a key stakeholder. The good news is that there is not much language in the regulations specifying the content and style of procedures[1]. There are no statements that preclude or undermine the use of new technology in this space. The primary requirement is that they be **clear**. There seems to be some discretion as to which kinds of activities require a procedure ("as applicable"). The key element is that we need to be able to demonstrate the robustness of our procedures to regulators – including ones developed for electronic media. This will entail additional effort but it is possible. With electronic implementations, record keeping and presentation to the FDA should be more efficient and transparent as long as they are bought into the system. Additionally, better quality enables better and smoother audits.

[1] EudraLex Volume 4 EU Guidelines Part I Chapter 4 Documentation

7.6.3 MPs and batch records

Currently a lot of overlap exists between MPs and SOPs depending on the plant you are looking at with many MPs containing instructions that ought to belong in SOPs. Amgen needs to develop a clear demarcation between what is in the MP (recipe and records) and the SOPs (instructions on how to perform each step the MP demands). Our new vision clarifies what belongs in the SOP and does not – this will make it easier for authors of MPs to ensure that clear boundaries are set with SOPs. The focus of this project is not on MPs though our research indicates that MPs and batch records could benefit from applying some of the thinking we are applying to SOPs. However, most MPs are fairly organized due to recording requirements set by inspectors from the FDA.

7.7 Changing the culture of procedures

Since the performance of SOPs depends completely on how people interact with them, there are certain cultural behaviors and norms that need to be aligned to ensure the success of our future vision.

Consistent expectations: We have procedures for almost every kind of operation, from the high frequency routine (gowning) to the lower frequency critical (bioreactor). We tell our operators that we require them to use the procedure for *every task they perform*. Yet, in practice we provide confusing expectations when it comes to procedure adherence. Though gowning and chromatography both have SOPs, we do not fault operators for not having their SOPs out and open while gowning. This provides an inconsistent message on procedure use.

We need to provide a consistent and clear message on expectations for using procedures. If a certain task does not need a procedure out and open during the task, then the information required for that task needs to be carefully considered. In those circumstances, a reference guide or other type of instruction should be

provided. While we can often get hung up on the nomenclature, it is not as important as ensuring we provide a clear and consistent message to staff on which procedures need to be followed for which jobs and in what fashion. Without that clarity, we introduce too much uncertainty and discretion into our work processes.

Operator buy-in: A great set of procedures is not any good if the operators do not use them and do not believe they add value. This needs to be addressed in two ways:

- Engage the operators in the authorship of the procedures: The best way to ensure that you are meeting the needs of your audience is to involve them in the development process.

- Make the procedures relevant: If the procedures are distilled down to their essence, then they become easy to use and the operators are more likely to use them every time. Irrelevant information dilutes the importance of the procedure in the mind of the operator.

By ensuring we consider these cultural aspects of our organizational change (as outlined above), our new initiative will be better received by management and staff and ensure a smooth transition from the old style of SOPs to the new.

7.8 Electronic media

In discussions with staff on the subject of procedures, the enthusiasm surrounding moving towards more electronic/high-tech methods was considerable. The iPads already present at a number of facilities are very popular and effective.

Yet, we have yet not taken real advantage of the electronic media. At best, they currently serve as a library for paper information – a binder replacement (‘paper on glass’). Given the immense potential to develop solutions using computers we can consider many more possibilities:

- **Applications:** Imagine an application that can guide an operator through the critical steps in his process. This application can be a repository of tremendous amounts of information that can be retrieved at the key moments based on defined triggers or operator input/request. This is something completely separate from the paper procedures, but a fully interactive application that walks the operator through every required step.

- **Training integration:** Electronic training systems can be integrated into the procedure system. Operators who have not completed the required training will not be able to access the procedure for that particular job. This introduces an additional level of compliance in the process.

- **Manufacturing Procedure/Batch Record integration:** If all MPs were electronic, they would not need to be separate from procedural documents. All instructions could be embedded in the application through screens/prompts. Any entry points could be made into the computer at the right time – in fact the system would prevent advancing steps without entering the requisite data, a quality improvement. Data entered into the system could be dumped out into any kind of FDA friendly format potentially eliminating a large amount of paper. Imagine a system where instruction, entry and reports are all integrated into one electronic system that is all available through your tablet allowing the operator to deal with one interface instead of many.

- **Videos:** The ability to watch someone else perform a task before performing it yourself can be a great learning tool. The electronic format allows us the ability to present videos as the procedure or as part of the procedure.

- **Revision control:** Currently, it is a non-trivial effort to ensure every operator is trained on the most up to date version of the procedure. In an electronic system, you can point all requests for

information to a central source where the most current approved revision resides. Outdated revisions are electronically archived to prevent confusion and operators can only access the most up to date version of the procedure.

- **Eliminate paper:** Not only is it in alignment with environmental sustainment objectives, but in many circumstances it is more efficient to use and share information.

With this electronic implementation, we are moving away from 'paper on glass' (where electronic media simply display the same content and formatting as seen on paper procedures). Instead of an expensive binder replacement, electronic tools will be used to present task critical information in new and more intuitive ways. Electronic procedures do not equate with reading a word document or pdf on screen.

It is important to note that any widespread electronic implementation will require considerable investment of time, money and effort. A number of the solutions require newer technologies and approaches to be developed. There are a number of considerations:

1) Cost to develop new technical infrastructure
2) Cost to train current workforce to use technology
3) Growing pains
4) Cost to train procedure developers to use new technology
5) Cost to integrate or upgrade connecting systems.

These are real costs but considering the rest of the world is moving in this direction, this cost will have to borne sooner or later. It is important to get ahead of this leading trend to capture the market advantages as opposed to being left behind and losing competitive edge.

8 Pilot project

This chapter discusses our efforts to pilot some of the ideas we discussed in the last chapter in a real biomanufacturing environment. We discuss the process of scoping out the pilot project, developing prototypes, selecting metrics and deciding the parameters for the experiment. The goal of this pilot was to test our hypothesis (that our new SOP vision will have positive impacts on manufacturing performance metrics) within certain constraints.

8.1 Scope

The pilot project was designed to test our hypothesis in a live manufacturing environment. In order to effectively test our ideas, we needed to be able to

1. Identify a portion of a working manufacturing plant suitable for pilot activities
2. Baseline current SOP performance along identified performance metrics
3. Replace the current SOPs with new SOPs based on our new approach
4. Measure the impact of new SOPs performance against baseline
5. Analyze the data and evaluate our hypothesis

Since we desired to measure the impact of new SOPs, we limited the extent of our changes to just the SOPs. We endeavored to control against changes in the other aspects of the process (MPs, operational improvements, equipment change overs, turnover, etc.) as much as possible to delineate out the impact of new SOPs. We also wanted the pilot to test out each type of new SOP to see if any one method was superior to another and account for weaknesses any individual SOP would have on the overall experiment. Lastly, to ensure we were consistent with our principle of user oriented design, we ensured that key operators were deeply involved in the development of new SOP prototypes.

8.2 Site selection

During the selection process for the pilot project site, we evaluated a number of different manufacturing facilities within the Amgen network. We evaluated both clinical and commercial facilities over a number of different geographies. Ultimately, we ended up choosing the buffer preparation cell in Plant A for the following reasons:

1) **Proximity:** Plant A was close to where our team was operating from and as such made it easier for planning and monitoring purposes
2) **Clinical plant:** Unlike commercial manufacturing plants, clinical plants tend to be better at dealing with changing processes since they routinely change their product mix. Additionally clinical plants have a little more leeway with the regulatory bodies since the product is not being sent straight to the public.
3) **Improvement opportunities:** This buffer prep area in Plant A had already been identified by management as having SOP and document challenges. Additionally, the buffer prep area was occasionally the bottleneck in the process. These two reasons allowed management to support bringing major changes to SOPs in this area. With any pilot project, local management support is key.
4) **Throughput:** Unlike many other areas in biomanufacturing, buffer prep has a lot of production runs. Buffers are constantly being batched every week for different products. This allowed us to be able to collect a significant amount of data within a shorter timeframe. The throughput was still less than traditional mechanical manufacturing (e.g. automobiles), but is on the higher side of biomanufacturing processes.
5) **Risk exposure:** The risk exposure from buffer prep to product quality and patient safety is relatively low. This is important hurdle in getting approval from management to conduct pilot activities of such dramatically new processes.

6) **SOP variety:** The buffer prep area in Plant A had enough variability in complexity of the tasks required that we would be able to pilot all the different types of SOPs we wanted to test.

8.3 Prototype development

Our team worked closely with the operators in Plant A to develop a new set of SOPs for the buffer prep area. We initially made a list of all SOPs associated with the buffer prep area. However, not all these SOPs were relevant for day-to-day execution so we collapsed this list to the relevant SOPs. Then we compared the SOPs to the tasks actually performed by the operators. Based on that, some SOPs were either combined or split based on the needs of the individual task they were addressing. Our goal was to have one SOP per task (moving away from equipment based SOPs). Once we had determined the scope of the SOPs required for the buffer prep area, we set out to build the new SOPs from scratch based on:

- The content required to be communicated based on relevant information from the old SOP and input from operations
- The best way to communicate the content based on the nature of the task and input from operations

We then developed storyboards (simple mock-ups) of what the new SOP design would look like to share with stakeholders for initial approval and endorsement.

Wetting of Filters

Filter Material/Item#	Inlet Pressure	Minimum time of flushing	Flow Rate L/min
2843 FF	40 psig at Ambient °C	5 minutes	7.5
Mustang Q XT5000 (30000084)	5±1 psig at Ambient °C	13 minutes	8-10

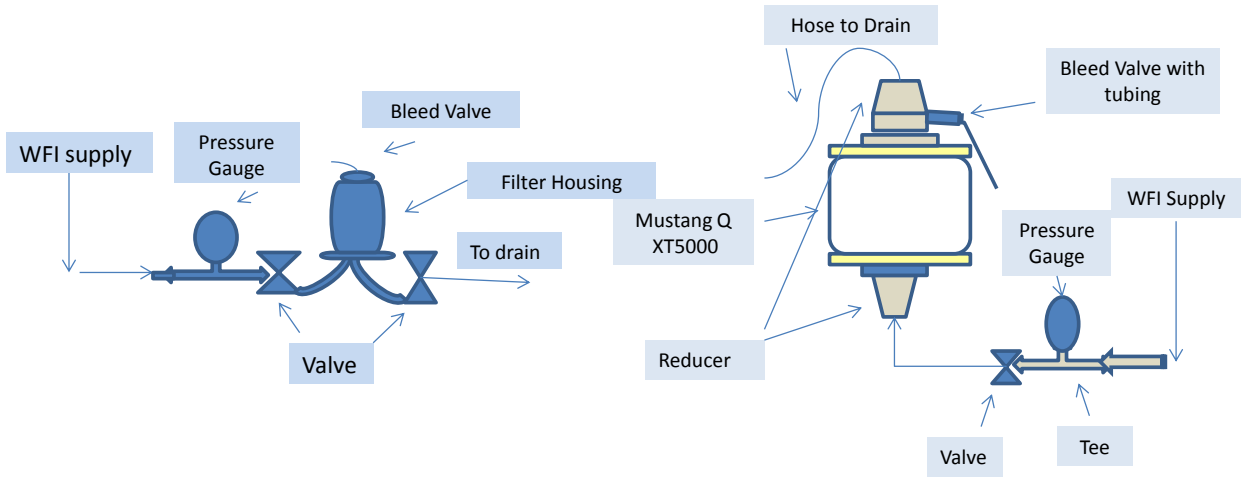


Figure 13: Example storyboard

For the more complex tasks (e.g. the fixed tanks SOP) slated to be converted into an electronic SOP, we developed detailed process maps and flowcharts to ensure that the electronic SOP would capture all the relevant decision points in the process.

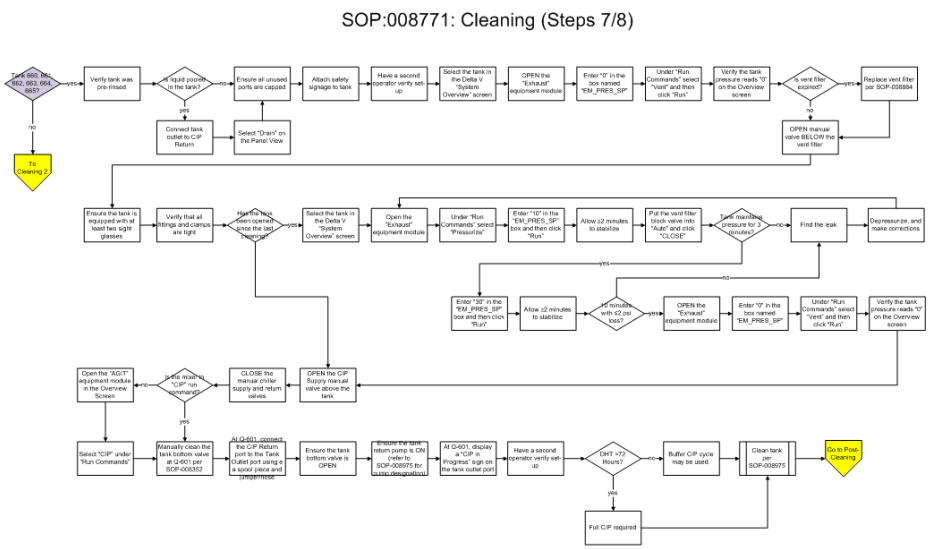


Figure 14: Example flowchart

The Electronic SOP for fixed tanks was originally intended to be developed as an iPad application that could be installed on the iPads used by operators on the floor. However, resource constraints forced our team to develop a mock-up in Microsoft PowerPoint. This mock-up behaved like an interactive iPad application so it allowed us to test the user experience with electronic SOPs for the purposes of our pilot. Screenshots from the electronic procedure can be found in the Appendix.

The last step in the process was to submit all the new SOPs for review by Quality to ensure we had not removed any relevant information from the SOPs in our new design. At the end of our process we decided to pilot the following SOPs:

- Fixed tanks (Electronic SOP): An extremely complicated procedure with lots of decision trees in its instructions, we felt this would benefit the most from moving to an electronic SOP. By mapping out the decision logic in the technology, we allow the operator to only receive the relevant instructions based on their inputs into the program. This way, they do not have to parse through every path in the decision tree to find the one relevant to them.

- Filters assembly (Diagram SOP): A procedure completely reliant on an operator's ability to assemble filters and their wetting setups, this visually driven SOP was a considerable enhancement over its predecessor. By using detailed diagrams, we were able to represent the same information with more clarity and highlight key technical information.
- Conductivity and pH calibration (Instruction SOPs): These two procedures were classic examples of simple procedures with too much detail. The most relevant portions of the procedure dealt with the operator interacting with the calibration PLC. An Instruction type SOP is perfectly suited to the task.

8.4 Metrics

To test our hypothesis, we want to evaluate if our new SOPs have positive impacts on key manufacturing metrics: productivity, quality and compliance. Not all of these metrics were directly measurable from our process. In this section, we will discuss the different metrics we considered, their pros and cons and why we did (or did not) end up selecting them for the pilot.

8.4.1 Quantitative

1. **Takt time:** This is the time taken by an operator to complete a task. This is a useful measure for those tasks where there is little wait time built into the system and there is an incentive to finish the task as fast as possible. For certain operations, takt time is an excellent proxy for productivity and as a result we selected it as a metric. It is measured manually by operators.
2. **Deviation from target:** For certain tasks, we look to achieve a certain target level or performance to meet specification. Calibration of meters is a good example. We considered measuring deviations to this target for to track improvement in such tasks. However, historical data indicates that calibrations

rarely are off target. Additionally, it is difficult to control for external factors beyond the control of the operator that could affect calibration (e.g. machine performance and chemical accuracy of standard solutions). We did not select this metric.

3. **Non Conformances:** NCs are an important metric quality uses to measure adherence to quality standards. However because Amgen operates its plants to standard, NCs are not a frequent occurrence; not frequent enough to tell us any measurable information during the pilot project. Chances were that we may see only one or two NCs during our project timeframe (on the order of a few weeks at most). We did not select this metric.

8.4.2 Qualitative

Outside of the quantitative metrics we were going to collect for the pilot, we decided we were going to seek qualitative feedback from the operators as well. Information on how much they liked (or disliked) the new procedures and how easy they were to use were good secondary proxies for compliance and in some cases productivity. Qualitative information was collected through an anonymous survey.

In total we decided to measure takt time and qualitative feedback as our metrics. Given the constraints of the local plant and the pilot program, these were the best proxies we could use for productivity, quality and compliance. Similar experiments with more flexibility might be able to use some of the other metrics we discussed in this section. In the next chapter, we present the results of our pilot.

9 Results

This chapter presents the results we were able to obtain from our pilot efforts. Based on the constraints of the manufacturing organization and other external factors, we were only able to collect reasonable data for diagram procedures (filter assembly and testing setup). We were not able to collect extensive data about electronic SOPs and instructional SOPs. However, the data we did get does provide valuable lessons and soft indicators on performance of these SOPs in conjunction with informal feedback.

9.1 Filter assembly and wetting setup

In this experiment, we asked operators to assemble the filter as well as the surrounding assembly required for testing the integrity of the filter (more commonly referred to as 'wetting'). This is standard task that operators are required to perform based on the guidance in their SOP. This test featured our new diagram SOP for filters. We used quantitative and qualitative measures to measure performance of our new SOP against the current offering. This test was done not as part of regular operations but offline in a simulated environment. A number of operators participated in the exercise with experience ranging from a few weeks to 13 years.

9.1.1 Quantitative Results

We measured the time taken to perform the task correctly with the old SOP versus our new SOP. Below, Figure 15 shows the improvement in time with our new SOPs for new/relatively inexperienced operators. Figure 16 shows the improvement in time for experienced operators.

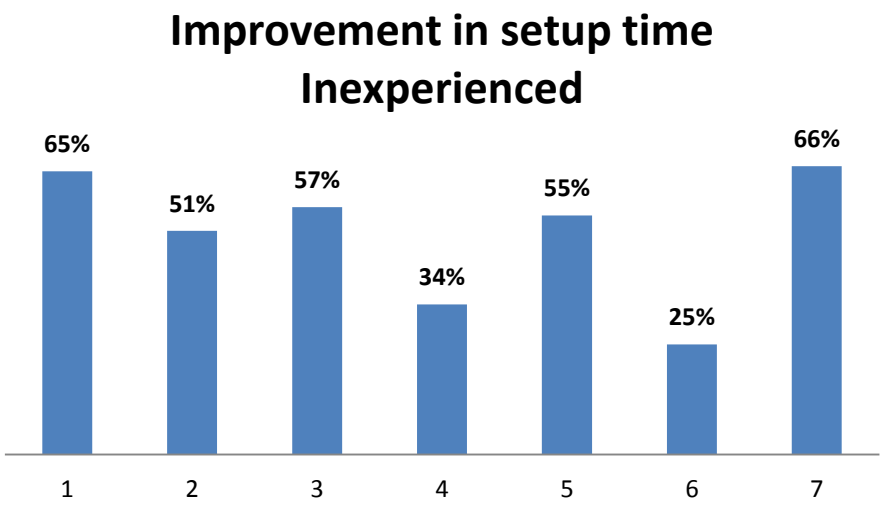


Figure 15: Productivity improvement for inexperienced operators

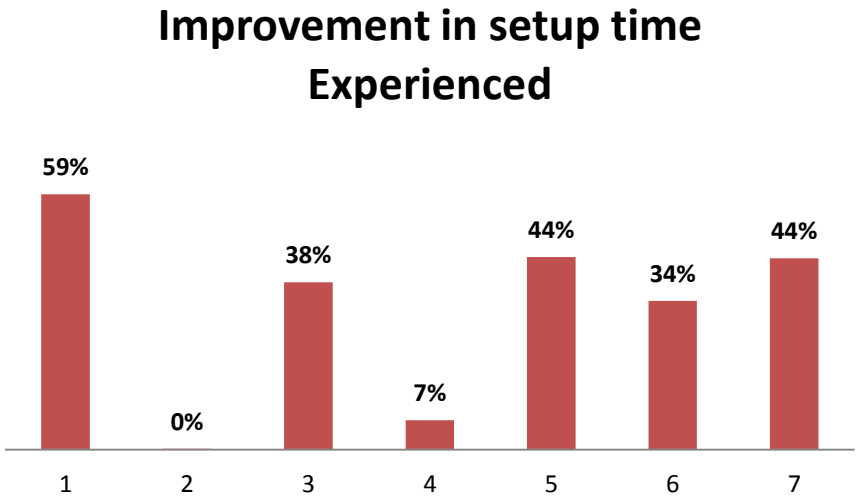


Figure 16: Productivity improvement for experienced operators

All inexperienced operators and the majority of experienced operators achieved significant productivity gains using the new SOPs. In fact, one of the inexperienced operators was unable to complete their task using the old SOP and abandoned the effort (not included on graph). On average, experienced operators' productivity improved by **32%** and inexperienced operators' productivity improved by **51%**.

9.1.2 Qualitative results

The qualitative feedback from operators was largely positive. Below are some our findings from the survey:

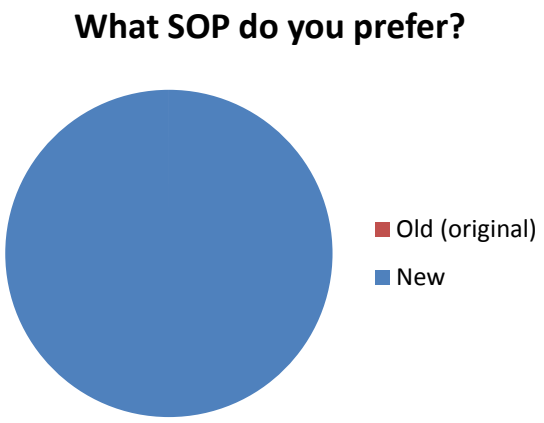


Figure 17: SOP preference

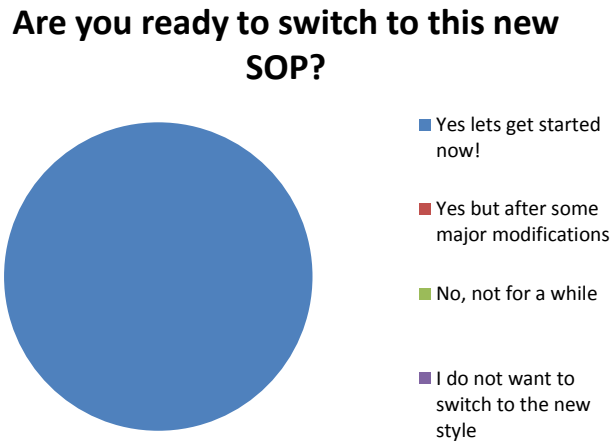


Figure 18: SOP preference II

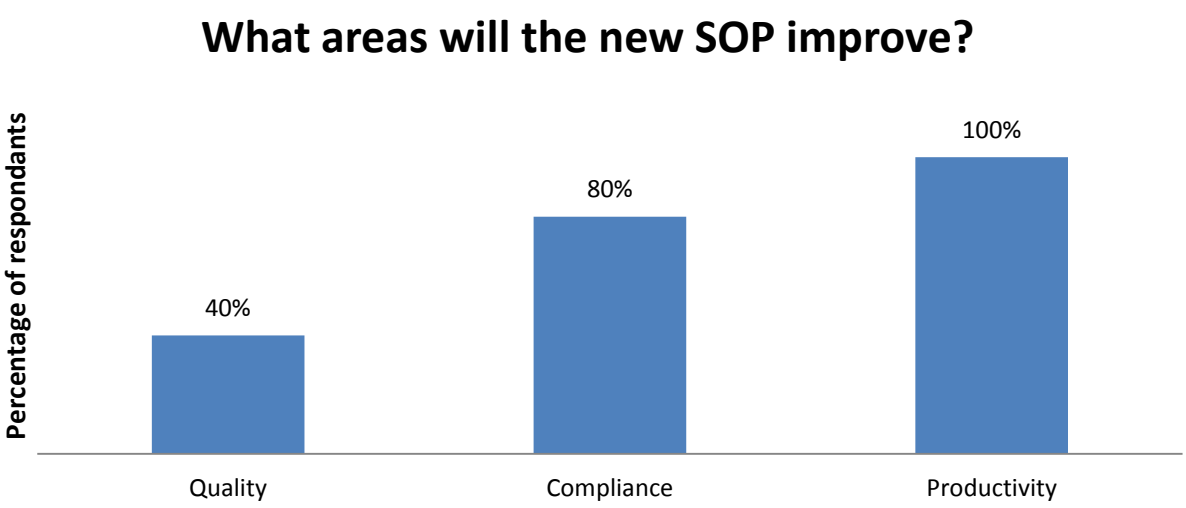


Figure 19: New SOP impacts on key metrics

Feedback indicates that adopting the new SOP philosophy will have a positive impact on major operational metrics. Along with the information above, we requested operators to provide written feedback about their experience with the new SOPs. Some excerpts are below:

- *"It was **far simpler to follow** ...with the second of the 2 [SOPs tested] it would be nearly, if not completely, impossible to perform without additional training [using old SOP]"*
- *"It is **clear, concise and specific** to my needs"*
- *"The information needed to perform the flushing process is **all in one place** in the new SOP. It was taking me a considerable amount of time to reference multiple places in the old SOP to find the relevant information. In addition, the new job aid contains a picture that details exactly the process that I will be performing. This greatly simplifies the task and **better represents the task**"*
- *"I think this type of SOP will also be extremely **beneficial in the training of new employees**"*
- *"This new procedure should be implemented immediately. It is obviously a much better procedure and **I wish I had access to it now**"*
- *"I preferred all aspects (visual, shorter length, task focused) of the new SOP. **There is nothing I do not like.** The new format saves substantial time and confusion"*

Overall, operator feedback for the new diagram SOPs for filters is positive and correlates well to the results we see in the time studies.

9.2 Fixed tanks

As discussed in the previous chapter, the fixed tank SOP is a complicated procedure involving multiple pieces of equipment, setup sequences and product requirements. This makes it an ideal candidate for an electronic procedure implementation. We tested the performance of this new SOP by allowing operators to use it in-line during regular operations instead of using their existing SOP. The existing SOP was available for reference (a requirement from the quality group), but the guidance was that operators were to use our new SOP during normal operations. A brief training session was provided where functionality of the electronic SOP was demonstrated to the entire operations staff and line management. As with the filters SOP, we aimed both qualitative and quantitative measures to evaluate performance. All staff working in the buffer prep area participated in this exercise.

9.2.1 Quantitative results

As with the filters, to measure productivity we used time studies. Since there is float time between individual steps, we measured the duration of each step where applicable. By measuring the actual takt time of each step, we can approximate decrease in time for improvements in productivity (ignoring external variables). We collected data for two weeks with our new SOPs and compared it to data we obtained from a one week baselining exercise. Due to constraints with the manufacturing plant, we were unable to run the pilot to collect a significant amount of accurate data. Some of the findings are presented below:

MP 6181	Batching time	Filtration time	Sampling/ Testing time	Triple rinse time
Baseline Vs Run 2 a	-52%	-62%	50%	-33%
Baseline Vs Run 2 b	117%	-11%	138%	-17%
Baseline Vs Run 2 c	79%	-15%	88%	-100%
Baseline Vs Run 2 avg	48%	-29%	92%	-50%

Table 1: MP 6181 baseline-pilot comparison

MP 6215	Tank setup time	Batching time	Tank pressurization	Filtration time	Sampling/Testing time	Triple rinse time
Baseline Vs Run 1	27%	86%	650%	88%	400%	150%
Baseline Vs Run 2	-27%	71%	400%	63%	400%	150%
Run 1 to Run 2 improvement	-43%	-8%	-33%	-13%	0%	0%

Table 2: MP 6215 baseline-pilot comparison

The tables above provide information on how the time required to perform the task either improved or worsened (percentage change). In Table 1, we compare the baseline performance to three separate batches during the second pilot run. This particular product (MP 6181) was batched only once during the baseline but it was batched three times during the second pilot run. While we see improvement in some areas ranging from 11% to 100%, conversely we see times in other areas increase by over 100%. In Table 2, we see that for MP 6215, we perform poorly against the baseline. It is worth noting that there is an improvement between the first and second run indicating the classic learning curve. It is reasonable to expect that performance with new SOPs would continue to improve with subsequent runs as operators become comfortable with the new format and the procedures themselves undergo continuous improvement.

9.2.2 Qualitative results

We were unable to collect any significant qualitative data on electronic SOPs. Informal feedback from the floor indicates that these new procedures will certainly improve compliance though the design needs to go through a couple of iterations to work out any deficiencies.

9.3 Identifiable trends

Given the results we have presented, we can identify the following trends:

- Procedures have a real impact on productivity
- Operators prefer more user friendly procedures
- Offering operators procedures they prefer improves compliance performance
- Where possible, more visually driven procedures work better
- Diagram procedures offer concrete productivity gains over their traditional counterparts

In summary, the new SOP approach has the potential to have lasting impacts to key operational metrics: productivity, quality and compliance. However, due to the constraints of our pilot plant we were unable to conduct exhaustive testing to assess this hypothesis with statistical significance.

10 Conclusions and future work

In this chapter, we discuss the conclusions of our research and research opportunities for future projects in this area.

10.1 Conclusions

Our research led us to propose a new structure for SOPs and the surrounding ecosystem. Our hypothesis is that this new structure and vision will improve performance of the organization along key operational metrics: productivity, quality and compliance. We attempted to verify this hypothesis by piloting our new SOPs in a real manufacturing environment. Given the constraints of the pilot plant, we were unable to test the hypothesis conclusively. However, the findings we did get from the filter pilot provided an indication that our hypothesis is valid though further research is required. Admittedly, the results from the fixed tanks pilot are not as supportive of our hypothesis compared to the filters pilot. However, we feel that the additional complexity of the fixed tanks pilot did not match well with our limited testing time and with additional testing time we might have seen more encouraging results. We believe our methods can yield positive results with further research and testing. Our philosophy of user centered and task based procedures aligns with the needs of the organization as it moves towards becoming a High Reliability Performance (HRP) organization.

Amgen has an opportunity to dramatically improve human performance in operations by revamping their SOPs and the surrounding ecosystem to align with the approach we have outlined in this thesis.

10.2 Next Steps and Recommendations

At the conclusion of the project, the multidisciplinary steering team we created to manage the project direction was tasked with moving the project into the next phase. This consists of taking the

lessons we learned with our first few pilots and developing further and more rigorous pilots in commercial manufacturing locations. In addition, this team has the responsibility of developing a company-wide implementation plan for adopting our new SOPs. This initiative will proceed in conjunction to other key initiatives like the Global Qualification Program (for training) to ensure all parties are aligned.

At the final report out for this particular internship, we provided senior management with the following recommendations:

- Adopt philosophy of 'job-based' SOPs
- Bring the FDA along for the ride in order to mitigate any compliance risk
- Create a culture that allows discernment between NCs caused by SOPs and those caused by other factors in a safe environment
- Dedicate resources to authoring, managing and supporting SOPs. This group will be the enforcers of the new SOP philosophy
- Develop alternative venues for the extraneous information extracted from current SOPs to be available for reference
- Integrate SOP development closely with training and qualification programs
- Develop an overall technology architecture that integrates EBR, SOPs, training information, production data, etc.

Implementing these recommendations in a careful and systematic manner will help Amgen improve its SOPs across the board and truly embrace HRP.

10.3 Future Work

Through this thesis, we have had the opportunity to research into many different areas of human performance, biomanufacturing and process improvement. That said, there are a number of additional research topics that would add to the body of knowledge in this new area

- **Large scale pilot:** The pilot in our research was a small scale experiment testing a limited aspect of our vision. A large scale project (at a plant level) over a longer period would provide additional insight not only into the validity of our hypothesis but otherwise unnoticed areas of improvement as well. A larger pilot would allow for testing of the new SOPs across multiple different areas and technologies and measure variations in effectiveness.
- **Parameter analysis:** One can run more detail pilots for specific complexity (or other variables) of procedures to tease out if that is a critical factor for success. Understanding which parameters about procedures (length, complexity, format, medium, etc.) have to most impact on which metrics (productivity, quality and compliance) would allow us to learn more on how to design more tailored made procedures for specific instances.

11 Bibliography

About Amgen. Amgen Inc. Retrieved 2013-02-21.
< http://www.amgen.com/about/amgen.html>

- "An Introduction to Biotechnology". Retrieved 2013-02-21.
< http://biotechnology.amgen.com/>

"Defense in Depth in Nuclear Safety – A report by the International Nuclear Safety Advisory Group". International Atomic Energy Agency, Vienna, 1996.

"Current Good Manufacturing Practice (CGMP)" regulation from the Food and Drug Administration (FDA) [CFR 21, Section 211, Subpart F]. Retrieved 2013-02-18.

< http://www.fda.gov/Drugs/DevelopmentApprovalProcess/Manufacturing/ucm169105.htm>

Schein, E. H. (1996). "The three cultures of management: Implications for organizational learning". *Sloan Management Review, 38*, 9-20.

Smith, Sally A. "A Network Planning Process and Inventory Strategy for High-Mix Low-Volume Markets". MIT Press.

Reason, James. (1997). "Managing the risks of organizational accidents". Brookfield, VT: Ashgate.

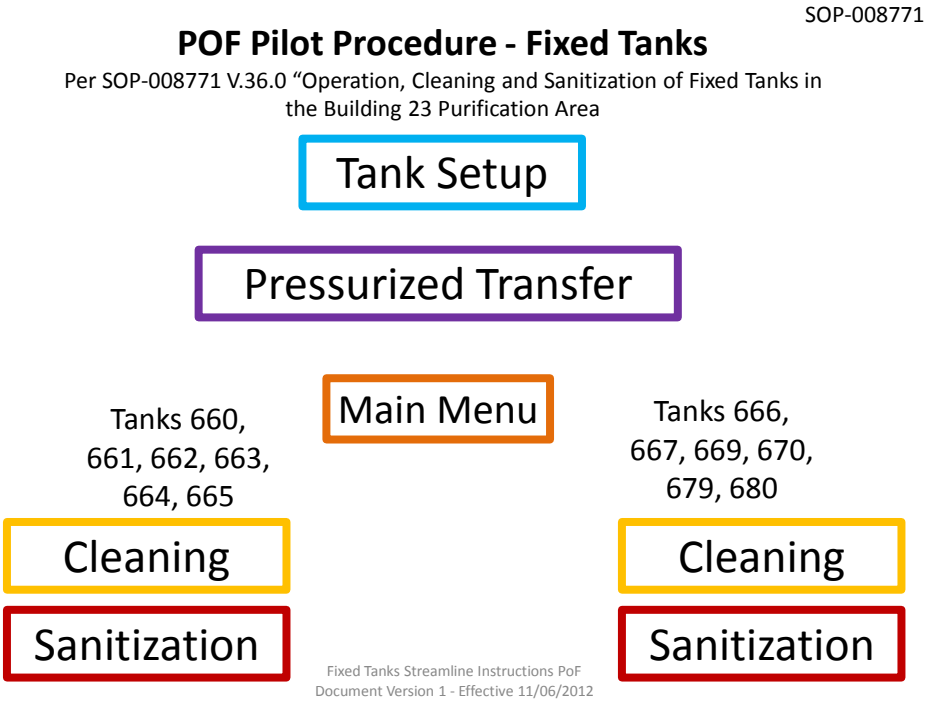
Constance Perin. (2006). "Shouldering Risks". Princeton U. Press, 2006

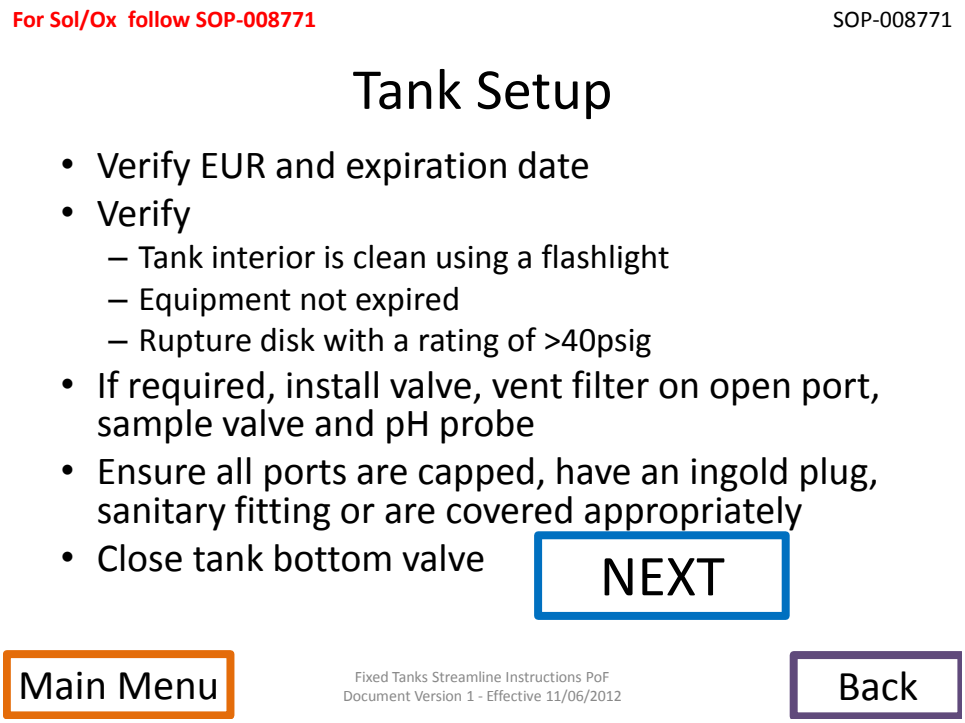
Mosneron-Dupin, F., Reer, B., Heslinga, G., Strater, O., Gerdes, V., Saliou, G., and Ullwer, W. (June 1997). "Human centered modeling in human reliability analysis; some trends based on case studies". Reliability Engineering and System Safety

Perrow, Charles. (April 1967). "A Framework for the Comparative Analysis of Organizations". American Sociological Review, Vol. 32, No. 2 (April 1967), 194-208

Smith, Alan B. (1998). "The A+B+C Method: A Technique for Achieving Optimum Balance of Three Critical Barriers to Human Error". MIT Press.

12 Appendix A – Electronic procedure screenshots





Is tank for product pooling?

YES NO

For Sol/Ox follow SOP-008771 SOP-008771

- Use dedicated dip tubes for tanks 669,670,679,680
- Otherwise dip tubes are optional for buffer procedures

amp1

AE1

NEXT

Is it T-660 T-661 T-662 T-663 T-664 or T-665?

YES NO

(Y)

- Verify
  - PRA supply valve is open
  - PCWS and PCWR isolation valves are OPEN
- Set over pressure regulator

NEXT

- Select tank in DeltaV System overview screen
- Open Exhaust equipment module
- Under Run Commands, select Pressurize
- Ensure appropriate safety signage is in place

NEXT

For Sol/Ox follow SOP-008771 SOP-008771

(N)

- Set over pressure regulator
- Position the divert valve to Back Pressure Regulator

NEXT